НАЦІОНАЛЬНА АКАДЕМІЯ МЕДИЧНИХ НАУК УКРАЇНИ
НАЦІОНАЛЬНИЙ НАУКОВИЙ ЦЕНТР РАДІАЦІЙНОЇ МЕДИЦИНИ

Кваліфікаційна наукова праця на правах наукової доповіді

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ДИСЕРТАЦІЯ

АНАЛІТИЧНІ ЕПІДЕМІОЛОГІЧНІ ДОСЛІДЖЕННЯ СТОХАСТИЧНИХ ЕФЕКТІВ ОПРОМІНЕННЯ В УЧАСНИКІВ ЛІКВІДАЦІЇ НАСЛІДКІВ АВАРІЇ НА ЧАЕС В УКРАЇНІ

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Дисертація містить результати власних досліджень. Використання ідей, результатів і текстів інших авторів мають посилання на відповідне джерело.

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АНОТАЦІЯ

Гудзенко Н.А. Аналітичні епідеміологічні дослідження стохастичних ефектів опромінення в учасників ліквідації наслідків аварії на ЧАЕС в Україні. Кваліфікаційна наукова праця на правах наукової доповіді за сукупністю публікацій

Дисертація на здобуття наукового ступеня доктора медичних наук за спеціальністю 03.00.01 – радіобіологія. Національний науковий центр радіаційної медицини Національної академії медичних наук України, Київ, 2021.

Дисертація присвячена розробці методичних підходів до проведення аналітичних епідеміологічних досліджень в Україні для достовірної оцінки реалізованих і потенційних ризиків виникнення стохастичних ефектів опромінення серед учасників ліквідації наслідків Чорнобильської катастрофи

Серед віддалених ефектів опромінення внаслідок аварії на Чорнобильській атомній електростанції (ЧАЕС) найбільші негативні очікування були пов’язані з можливим надлишком онкологічних захворювань. Перші повідомлення про наслідки радіаційного опромінення були опубліковані щодо осіб, які потерпіли внаслідок атомного бомбування цивільних міст Хіросіми та Нагасакі в 1945 р.. Серед перших медичних наслідків було зафіксовано суттєве дозозалежне зростання ризику всіх форм лейкемії, окрім хронічної лімфоцитарної (ХЛЛ). Пізніше було зафіксовано зростання ризиків окремих форм солідних пухлин, перш за все, раку щитоподібної та молочної залоз, легені та деяких інших. Найбільша частка надмірних випадків смерті від лейкемії серед осіб, які пережили атомне бомбування, була зареєстрована в перші 15 років після опромінення, хоча радіаційно асоційований надлишковий ризик лейкемії,

особливо її гострої мієлоїдної форми, реєструвався впродовж майже 60-річного періоду спостереження. Пізніше надлишок виникнення лейкемії та солідних пухлин був зафіксований в інших опромінених популяціях.

Представлені оцінки були отримані для осіб, що зазнали впливу опромінення у високих дозах протягом дуже короткого часу. Дослідження впливу тривалого або фракційного опромінення у малих чи великих дозах на зміну величини ризику лейкемії та інших злоякісних новоутворень (ЗН), результати яких виносяться на захист, не втрачають актуальності.

Загалом, всі відомі оцінки ризиків виникнення онкологічних наслідків і генетичних ушкоджень у осіб, які підпали під дію іонізуючого випромінювання, базуються на даних аналітичних епідеміологічних досліджень в опромінених популяціях: в когорті свідків атомного бомбування в Японії (Life Span Study cohort), когортах працівників виробництва «Маяк» і мешканців населених пунктів вздовж річки Теча (Techa river cohort), а також когорті працівників атомних електростанцій країн Північної Америки та Європи і серед осіб, опромінених за медичних потреб. Таким чином, розробка і запровадження методів адекватного планування та реалізації аналітичних епідеміологічних досліджень в Україні дозволить достовірно оцінити ризики, спричинені опроміненням внаслідок аварії на ЧАЕС.

Учасники ліквідації наслідків аварії (ЛНА) на ЧАЕС являють собою чисельну популяційну групу переважно осіб чоловічої статі виробничо і соціально активного віку, які, були опромінені в широкому діапазоні доз. Серед постраждалих саме в цій групі можливо дослідити дозо залежний ексцес ризику злоякісних новоутворень, якщо він взагалі існує у зв′язку із Чорнобильською катастрофою.

В роботі акцентується увага на основних методичних принципах планування аналітичного епідеміологічного дослідження і на досвіді їхньої практичної реалізації для оцінки ризиків лейкемії, раку щитоподібної залози (РЩЗ) та можливих спадкових генетичних ушкоджень серед

учасників ліквідації наслідків Чорнобильської катастрофи в Україні. Лейкемії як ефект впливу іонізуючого випромінювання на організм людини характеризуються найбільшою чутливістю до цього фактору з усіх відомих стохастичних ефектів, найменшим латентним періодом та найбільшою амплітудою відхилення ризиків від популяційного рівня. Надлишок РЩЗ може маніфестувати слідом за лейкемією, переважно серед опромінених в молодшому віці. В той же час, існувала ймовірність надлишкової захворюваності серед учасників ліквідації наслідків аварії, яка була доведена в описових (дескриптивних) роботах і потребувала підтвердження в аналітичному дослідженні ризиків РЩЗ, яке було реалізовано за методикою випадок-контроль.

Метою роботи було розробити та практично застосувати комплексну методологію аналітичного епідеміологічного дослідження стохастичних медико-біологічних ефектів іонізуючого випромінювання в Україні та визначити ризики виникнення віддалених онкологічних і генетичних ушкоджень внаслідок опромінення під час ліквідації наслідків Чорнобильської катастрофи.

Перший розділ роботи було присвячено аналізу стану проблеми вивчення стохастичних ефектів опромінення після аварії на ЧАЕС в Україні, результатам дескриптивного аналізу проблеми та обгрунтуванню аналітичних епідеміологічних досліджень серед учасників ЛНА. За наведеними даними описових досліджень (підрозділ 1.1) констатовано наявність зростання захворюваності на РЩЗ в кожній із груп постраждалих із найбільш суттєвими значеннями для учасників ліквідації наслідків Чорнобильської катастрофи, рівень захворюваністі (стандартизоване співвідношення рівнів, SIR) серед яких був в 5,9 раза вищий за національні показники в 1994–2006 рр. із подібними величинами за період спостереження 1994–2012 рр.

В іншому описовому дослідженні (підрозділ 1.2) порівнювалась захворюваність на РЩЗ населення територій, забруднених радіонуклідами.

Значення середньої кумулятивної дози опромінення щитоподібної залози, вищі і нижчі за 35 мГр, послужили граничним значенням розпорділу між теритоіями «з низькою експозицією» і з «високою експозицією» з подальшим порівнянням захворюваності населення на РЩЗ на цих територіях. Було визначено найбільшу чутливість до радіаційного впливу, щодо виникнення РЩЗ, осіб, народжених у 1982–1986 роках, тобто у віці 0–4 років на момент аварії на Чорнобильській АЕС на територіях з «високою експозицією».

Також в першому розділі дисертації (підрозділ 1.3) представлено основні висновки групи «Health» Чорнобильського форуму (спеціально сформованої міжнародної експертної групи під егідою 8 інституцій ООН, в склад якої входила і автор дисертаційної роботи). Було констатовано відсутність впродовж 20 післяаварійних років підтверджених доказів ефектів опромінення внаслідок аварії на ЧАЕС щодо лейкемії, РЩЗ та інших форм раку в групах опромінених осіб, в тому числі серед учасників ліквідації наслідків аварії. Єдиним доведеним медичним ефектом аварії було визнано РЩЗ серед опромінених мешканців найбільш забруднених радіонуклідами територій наймолодшої вікової групи.

Разом з тим, для отримання обгрунтованих висновків була визначена необхідність проведення аналітичних епідеміологічних досліджень і підтримки діяльності популяційних реєстрів, перш за все національних канцер-реєстрів.

Другий розділ присвячений розробці дизайну та обгрунтуванню складових доказового аналітичного дослідження

Було визначено і деталізовано найважливіші складові якісного аналітичного епідеміологічного дослідження для забезпечення доказовості отриманих результатів.

Вони полягали унаступному:

1) адекватній потужності дослідження з урахуванням відповідних характеристик обраної досліджуваної когорти, дизайну дослідження, переліку захворювань для вивчення, періоду спостереження;

2) ідентифікації випадків захворювання у повному обсязі і з гарантованою верифікацією діагнозів;

3) виборі адекватного методу дозиметрії, який відповідає характеру опромінення, та визначеним критеріям якості

Прийнятний рівень статистичної потужності дослідження лейкемії, не менший за 80 %, був забезпечений розміром обраної когорти (110 645 осіб чоловічої статі), періодом спостереження (15 років і більше), та можливим рівнем відносної біологічної ефективності опромінення внаслідок Чорнобильської катастрофи від 0,25 до 1,0, порівняно із когортою опромінених унаслідок ядерного бомбування в Японії.

Пізніше для дослідження раку щитоподібної залози когорту було збільшено до 150 813 осіб зі збереженням необхідної потужності дослідження.

Третій розділ роботи присвячений методичним підходам до пошуку, ідентифікації та верифікації діагностичних даних про захворювання в повному обсязі. В першому підрозділі описано процесс ідентифікації випадків раку щитоподібної залози для проведення SIR аналізу захворюваності на РЩЗ.

Випадки РЩЗ було ідентифіковано за процедурою детерміністичного з елементами ймовірнісного лінкіджу даних файлу когорти із базою даних Національного канцер-реєстру. Таким чином було ідентифіковано 196 випадків раку щитоподібної залози, які слугували основою для аналізу захворюваності на РЩЗ в досліджуваній когорті. Розрахований стандартизований за віком показник захворюваності на РЩЗ в досдіджуваній когорті (SIR) впродовж 1986–2010 склав 3,50 (95% довірчий інтервал (ДІ): 3,04–4,03).

Щодо верифікації діагнозів випадків раку щитоподібної залози, враховувався рівень гістологічного підтвердження цих захворювань (97,5 %), заявлений в офіційно опублікованих бюлетенях Національного канцер-реєстру України (НКРУ).

Другий підрозділ присвячено процедурі і результатам незалежної міжнародної гістологічної верифікації діагнозів лейкемії і споріднених захворювань. Результати експертизи визначили задовільну якість та доступність діагностичних матеріалів в досліджуваних регіонах України. В цілому було підтверджено діагнози в 49 (79%) із 62 випадків, представлених на перегляд. В тому числі, було підтверджено 34 (89 %) із 38 випадків лейкемії. 4 основні сесії експертизи в подальшому проходили за методологією у точній відповідності із попередньо протестованою.

В четвертому розділі надано характеристику обраним методам дозиметричного супроводу аналітичного дослідження стохастичних ефектів радіаційного впливу в результаті виконання ЛНА на ЧАЕС.

RADRUE було обрано із переліку протестованих методів для відновлення дози зовнішнього опромінення на цільовий орган або тканину (на червоний кістковий мозок для суб’єктів дослідження лейкемії, на тканину щитоподібної залози у відповідному проекті, або на гонади в дослідженні генетичних ушкоджень, які могли передатись наступному поколінню від опромінених учасників ЛНА) .

За результатами проведеного дослідження, було доведено заявлені чутливість і універсальність методу, за допомогою якого було відновлено дози для 112 померлих і для 888 живих суб’єктів дослідження ризиків лейкемії, хоча із 162 ідентифікованих випадків лейкемії дозу опромінення вдалось реконструювати тільки для 137 (84,6%).

Центральні оцінки дози на червоний кістковий мозок (**підрозділ 4.1**) варіювали від 3,7 10^{-5} до 3 260 мГр, середня арифметична яких склала 92 мГр., в тому числі 132,3 мГр для випадків і 81,8 мГр для контролів.

В другому підрозділі представлено дозиметричні підходи, використані в дослідженні раку щитоподібної залози.

Зважаючи на те, що в індукції раку щитоподібної залози , окрім зовнішнього, суттєву роль може відігравати внутрішнє опромінення цього органу за рахунок інгаляції ^{131}I і короткоживучих ізотопів I і Te, для відновлення цього компоненту дози було розроблено спеціальні математичні моделі для аналізу даних додаткових розділів анкети, які заповнювались під час інтерв'ю із суб'єктами дослідження.

Середня арифметична дози опромінення щитоподібної залози з урахуванням всіх шляхів експозиції склала 199 мГр (діапазон від 0,15 мГр до 9,0 Гр)

П'ятий розділ присвячено оцінкам дозозалежних ризиків виникнення досліджених онкологічних ефектів опромінення внаслідок аварії на ЧАЕС.

В першому і другому підрозділах представлені визначені оцінки ризику лейкемії впродовж двох етпаів дослідження

Статистичний аналіз було проведено застосовуючи модель умовної логістичної регресії (conditional logistic regression model). Було визначено лінійну достовірну позитивну асоціацію між кумулятивною дозою опромінення на червоний кістковий мозок з урахуванням 2–хрічного лаг-періоду з надлишком відносного ризику виникнення лейкемії на 1 Грей опромінення (ERR/Gy), який в 1986–2000 рр склав 3,44; 95% ДІ: 0,47–9,78, $p<0.01$, а впродовж1986–2006 рр. – 2,38 з 95 % ДІ від 0,49 до 5,87 та $p=0,004$. Залежність «Доза-ефект» була подібною і мала позитивні значення як для для ХЛЛ (ERR/Gy=2.58, 95% ДІ: 0,02–8,43, $p=0,047$), так і для не-ХЛЛ групи лейкемій (ERR/Gy=2,21, 95% ДІ: 0,05–7,61, $p=0,039$).

Популяційний атрибутивний ризик виникнення лейкемії (PAR) склав 16,4 % (95 % ДІ: 3,9–32,6).

Третій підрозділ присвячено результатам оцінки впливу модифікуючих факторів нерадіаційної природи.

Єдиним фактором, вплив якого було оцінено як досить суттєвий для виникнення лейкемії, було визначено професійний контакт із бензином. При цьому встановлено, що надлишок ризику спостерігається за рахунок хронічних мієлоїдних форм лейкемії

В четвертому підрозділі висвітлено перші результати оцінки ризиків виникнення РЩЗ які констатують, що у когорті учасників ЛНА (150 813) визначено, хоча із граничною значимістю, надлишок відносного ризику виникнення цього захворювання впродовж 1986–2012 рр. (ERR/Gy]=0,40; 95% ДІ: -0.05, 1,48; p=0,12). Остаточні розрахунки ризиків РЩЗ внесені в рукопис манускрипту, який прийнято до друку в European Journal of Epidemiology і буде опубліковано найближчим часом.

Шостий розділ присвячено дослідженню генетичних ефектів опромінення серед нащадків учасників ЛНА на ЧАЕС та евакуйованих осіб.

Метою спільного американо-українського дослідження генетичних ефектів опромінення серед учасників ЛНА на ЧАЕС в Україні та їхніх нащадків (ТРІО) було дослідити геномні ушкодження в клітинах крові та епітелію ротової порожнини у звязку із дозою опромінення, отриманої батьками до моменту концепції, а також за 3 місяці до концепції. Доза була оцінена з використанням відповідних методів дозиметрії, основаних на аналізі даних персонального анкетування (RADRUE, його модифікація ROCKVILLE, математичне моделювання). Оцінювались можливі маркери генетичних ушкоджень, які могли передатись нащадкам опромінених батьків, насамперед де-ново мутацій, визначених шляхом секвенування цілого геному у опромінених батьків і їхніх нащадків, і оцінки надлишку їхньої частоти в залежності від дози на гонади батьків. За результатами проведеного дослідження було встановлено, що єдиним фактором, який суттєво впливає на рівень визначених де ново мутацій, був вік батька на час проведення дослідження. На поточний момент не було визначено залежності частоти де ново мутацій в учасників ЛНА та їхніх нащадків від

дози опромінення, отриманої батьками. Подальші дослідження із включенням більшої кількості суб'єктів можуть дійти уточнених висновків

Сьомий розділ присвячений результатам супутних поглиблених досліджень, ініційованих в досліджуваних когортах з метою визначення можливих особливостей перебігу або генетичних ушкоджень у випадках ХЛЛ, надлишок ризику виникнення яких було попередньо встановлено. Ці особливості могли сприяти виникненню або ускладненому перебігу захворювань.

Серед хворих ліквідаторів не було встановлено збільшеного числа мутацій в ХЛЛ–асоційованих генах порівняно із неопроміненими особами. Дослідження показало збільшення довжини теломер в пухлинних клітинах і мутації в генах підтримання теломер, які можуть відігравати певну роль в генезисі радіаційно–асоційованого захворювання на ХЛЛ, яке потребує подальшого вивчення. Аналіз даних щодо клінічних особливостей ХЛЛ в учасників ЛНА показав, що латентний період був суттєво коротшим у осіб, опромінених у більш літньому віці, у осіб, які палять, а також були старші за віком при встановленні діагнозу ($p < 0,05$). Достовірно вищим був ризик смерті у осіб, опромінених у дозі, вищій за 22 mGy, порівняно із опроміненими в дозі, нижчій за цей рівень. Виживаність була коротшою серед випадків ХЛЛ, опромінених в більш молодому віці і з вищим рівнем лімфоцитозу.

У **восьмому розділі** узагальнено результати епідеміологічних досліджень серед учасників ЛНА на ЧАЕС в Україні і визначено їхні перспектині напрями.

Ключові слова: аварія на Чорнобильській АЕС, учасники ліквідації наслідків аварії, стохастичні ефекти, надлишок відносного ризику, лейкемія, рак щитоподібної залози, генетичні ушкодження.

ABSTRACT

Gudzenko N.A. Analytical epidemiological studies of stochastic radiation exposure effects in Chornobyl clean-up workers in Ukraine. Scientific report. Collection of scientific manuscripts.

Thesis for a scientific degree of Doctor of Science in Medicine, speciality 03.00.01 – Radiobiology. National Research Centre For Radiation Medicine of National Academy of Medical Sciences of Ukraine, Kyiv, 2021.

The aim of the work was to develop and practically apply a comprehensive methodology of analytical epidemiological study in Ukraine to determine the potential and realised risks of stochastic effects due to radiation exposure in Chornobyl clean-up workers

The first section was devoted to the analysis of the state of the problem of stochastic effects of radiation after the Chernobyl accident in Ukraine, the results of descriptive study approaches in LNA participants and the substantiation of analytical epidemiological studies.

The second section is devoted to the development of design and substantiation of the components of evidence-based analytical research.

The most important components of a qualitative analytical epidemiological study are defined **in the second section** including ensuring acceptable study power, completeness and quality of case identification and adequacy of the selected dosymetry methods.

The **section 3** is devoted to the cases dentification procedure with the diagnoses verification in detailes. Alternative sources of personalized information on the cases of the studied diseases were used namely: databases of the state Chernobyl registry, National cancer Registry, leukemia register, created according to the data of regional and national medical institutions **(subsection**

3.1). Databases were linked to the studied cohort file by a specially developed software through deterministic (with elements of probabilistic) data linkage. **Subsection 3.2** is devoted to the diagnoses verification. The main stage of leukemia and related diseases verification is a two-stage (local and independent international) diagnostic expertise, which was first proposed and used. Quality of the thyroid cancer diagnoses was ensured by the officially published National cancer registry data on the rate of hystological verification.

Selection of adequate dosimetry methods are described in the **section 4** . RADRUE was selected from a list of tested methods to restore the dose of external radiation to the red bone marrow for subjects of leukemia, thyroid tissue or gonadas in the relevant projects. Central dose estimates for red bone marrow ranged from 3,7 10^{-5} to 3 260 mGy, with an arithmetic mean of 92 mGy, including 132,3 mGy for cases and 81,8 mGy for controls. For the internal portrion of the thyroid dose the special software programs were developed. The arithmetic mean radiation dose of the thyroid gland, taking into account all routes of exposure was 199 mGy (range from 0,15 mGy to 9,0 Gy).

Using the proposed methodology, the studies were completed and the risks of various forms of leukemia were analyzed, taking into account the influence of possible modifying factors. The results of the dose-dependent risks assessment are presented in the fifth section

Leukemia excess relative risk per 1 Gy of exposure in 1986–2000 was estimated to be 3,44; 95% CI: 0,47–9,78, p<0,01, including for cchronic lymphocytic leukemia (CLL) – (ERR/Gy = 4,09; 95% CI: not estimated–14,41) and for non–CLL leukemias (ERR/Gy = 2,73; 95% CI: not estimated–13,50). At the same time the ERR/Gy of leukemia for the period 1986–2006 accounting for two years LAG-period was assessed to be 2,38; 95 % CI: 0,49–5,87, p=0,004. Dose-response was similar for CLL cases (ERR/Gy=2.58; 95% CI: 0.02–8,43, p=0.047) and for non-CLL cases (ERR/Gy=2.21; 95% CI 0.05–7.61, p=0.039).

Altogether, 16% of leukemia cases (18% of CLL, 15% of non-CLL) were attributed to radiation exposure.

After adjusting for radiation, we found no clear association of leukemia risk with smoking or alcohol consumption but identified a two-fold elevated risk for non-CLL leukemia with occupational exposure to petroleum (OR=2,28; 95% CI: 1,13; 6,79). Risks were particularly high for myeloid leukemias. No associations with risk factors other than radiation were found for chronic lymphocytic leukemia.

The first conclusions about the excessive risk of thyroid cancer were obtained. It was idefined that in the clean-up workers cohort (150 813) there was an excessive Thyroid cancer risk in 1986–2012 at the following level: (ERR/Gy)=0.40; 95% CI: -0.05; 1.48; p=0.12, although with borderline significance. An article with final calculation of the of thyroid cancer risk is already submitted to the European Journal for Epidemiology, but on the date of the dissertation defense have not been published yet.

The **sixth section** is devoted to the study of the genetic effects of radiation among the descendants of persons exposed to radiation as a result of the Chernobyl accident as clean-up workers or evacuees. The methods used and the results of study are presented. The aim of a joint US-Ukrainian study of the genetic effects of radiation among participants in the Chernobyl disaster in Ukraine and their descendants (TRIO) was to investigate genomic damage in blood cells and buccal epithelium in each family member in relation to the radiation dose received by parents (participants in the liquidation of the accident or evacuated from the 30-km zone around the Chernobyl NPP) before the concept, as well as 3 months before the concept. The dose was estimated using appropriate dosimetry methods based on the analysis of personal questionnaire data (RADRUE, its modification ROCKVILLE, mathematical modeling). Possible markers of genetic damage that could be passed on to offspring of irradiated parents, primarily de-novo mutations determined by sequencing the entire genome in irradiated parents and their offspring in relation to the dose on the gonads of the parents were evaluated.

It was established that at the current moment there were no excess mutations associated with the radiation dose in the involved clean-up workers or evacuees families groups (parents and children / child).

The **seventh section** is devoted to the results of related in-depth research initiated in the studied cohorts

The first subsection presents the result of the study of possible dose-dependent genetic features of CLL that identified increases in telomere length in tumor cells and mutations in telomere maintenance genes that may play a role in the genesis of radiation-associated CLL disease.

The **second subsection** presents the results of a study of the clinical features of chronic lymphocytic leukemia in liquidators of the Chernobyl disaster. Analysis of the data showed that the latency period was significantly shorter in older people, smokers, and older people at diagnosis ($p<0.05$). The risk of death was significantly higher in individuals irradiated at a dose higher than 22 mGy compared to those irradiated at a dose lower than this level. Survival was shorter among cases of CLL irradiated at a younger age, with higher levels of lymphocytosis

The **eighth section** summarizes the results of epidemiological studies among the participants in the liquidation of the consequences of the Chernobyl accident in Ukraine and identifies their prospects.

Key words: Chornobyl accident, clean-up workers, stochastic effects, excess relative risk, leukemia, thyroid cancer, genetic damage

СПИСОК ОПУБЛІКОВАНИХ ПРАЦЬ ЗА ТЕМОЮ ДИСЕРТАЦІЇ

Наукові праці, в яких опубліковані основні наукові результати дисертації

Статті (фахові видання, віднесені до першого і другого квартилів (Q1 і Q2) відповідно до класифікації SCImago Journal and Country Rank або Journal Citation Reports)

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Інші статті (фахові видання, віднесені до третього квартиля (Q3) відповідно до класифікації SCImago Journal and Country Rank або Journal Citation Reports)

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ЗМІСТ

ПЕРЕЛІК ОСНОВНИХ ТЕРМІНІВ І СКОРОЧЕНЬ

Грей (Гр, Gy)	– Грей, одиниця поглиненої дози опромінення
ДІ, CI	– довірчий інтервал
ДРУ	– Державний реєстр України осіб, які постраждали внаслідок Чорнобильської катастрофи
Зв (мЗв)	– Зіверт (мілізіверт) одиниця ефективної дози опромінення
ЗН	– злоякісні новоутворення
ЛНА	– ліквідація наслідків аварії на ЧАЕС
МКХ-10	– Міжнародна класифікація хвороб десятого перегляду
НКРУ	– Національний канцер-реєстр України
РЩЗ	– рак щитоподібної залози
РЗТ	– радіоактивно забруднені території
ХЛЛ	Хронічна лімфоцитарна лейкемія
ЧАЕС	– Чорнобильська атомна електростанція
EAR	– надлишковий абсолютний ризик (Excess Absolute Risk)
ERR	– надлишковий відносний ризик (Excess Relative Risk)
LSS	– дослідження впродовж життя (Life span study)
RR	– відносний ризик (Relative Risk)
RADRUE	– Реалістична аналітична реконструкція дози з оцінкою невизначеності
SIR	– стандартизоване співвідношення захворюваності (standardized incidence ratio)

ВСТУП

Серед віддалених ефектів опромінення внаслідок аварії на ЧАЕС найбільші негативні очікування були пов’язані з можливим надлишком онкологічних захворювань. Першими з них реалізуються лейкемії, надлишок виникнення яких сигналізує про потенційне зростання захворюваності на інші форми злоякісних новоутворень (ЗН), в тому числі на рак щитоподібної залози (РЩЗ). Крім того, очікувались можливі ушкодження генетичного матеріалу, які могли передаватись наступним поколінням від опромінених осіб.

Такі очікування були зумовлені попереднім досвідом медичного спостереження за особами, які підпали під дію іонізуючого випромінювання внаслідок трагічних подій в Хіросімі і Нагасакі в 1945 р., діагностичних або терапевтичних медичних потреб, професійного опромінення, або внаслідок аварійних ситуацій. Перші повідомлення про наслідки радіаційного опромінення були опубліковані щодо свідків атомного бомбування цивільних міст Хіросіми та Нагасакі в 1945 р. [1–3]. Серед перших наслідків було зафіксовано суттєве дозо залежне зростання ризику всіх форм лейкемії, окрім хронічної лімфоцитарної (ХЛЛ) [1]. Пізніше було зафіксовано статистично значуще зростання ризику солідних пухлин в цілому [2, 3] із визначеним надлишком відносного ризику на 1 Зіверт опромінення (ERR/Sv) на рівні 0,63 та надлишком абсолютного ризику (EAR) 29.7 випадків на 10^4 людино-років Зіверт (EAR 10^4Sv). Надлишкові ризики були також визначені для окремих форм солідних пухлин (3) (раку шлунку (0,32), легені (0,72), кишківника (0,95), щитоподібної (1,15) та молочної (1,59) залоз, печінки (0,49), яєчника (0,99), шкіри (не меланома) (1,0) та сечового міхура (1,02)). Рак нервової системи (за виключенням раку мозку) серед опромінених у віці до 20 років, та рак слинної залози були також відмічені в переліку форм раку із надлишковим ризиком виникнення. Додатково проводився аналіз ризиків злоякісних новоутворень не тільки за даними захворюваності, але і за даними

смертності [4–6]. Надлишок відносного ризику, визначений за даними захворюваності, на 40 % вищий за такий, що визначений за даними смертності. В той же час надлишок абсолютного ризику в 2,7 раза вищий за даними захворюваності, ніж за даними смертності [5]. Тим не менш, рекомендовано використовувати обидва шляхи оцінки ризиків, адже вони надають комплементарну інформацію.

ERR/Sv серед осіб, які пережили атомне бомбування (хібакуші), у середньому, склав 9,1 3,3 і 6.2 для гострої лімфобластної лейкемії (ГЛЛ), гострої мієлобластної лейкемії (ГМЛ) і хронічної мієлобластної лейкемії (ХМЛ) відповідно. В той же час, в середньому, EAR для цих форм лейкемії склав 0,6, 1,1 і 0,9 випадків на 10^4 PY Sv відповідно. Функція доза-відповідь для ГМЛ була не лінійною, у противагу до всіх інших форм лейкемії [2].

Було визначено деякий надлишок захворюваності на лімфому серед чоловіків із визначеним EAR=0.6 випадків на 10^4 PY Sv, без подібного зростання серед жінок. Не було зареєстровано змін у захворюваності на множинну мієлому [2], хоча пізніше було встановлено незначний статистично значущий ексцес смертності з цієї причини серед жінок із зафіксованим ERR/Gy на рівні 0,86 (95% ДІ: 0,02, 2,5, p=0,04) [6].

Найбільша частка надмірних випадків смерті від лейкемії серед осіб, які пережили атомне бомбування, була зареєстрована в перші 15 років після опромінення [4]. В той же час, існують докази того, що радіаційно асоційований надлишковий ризик лейкемії, особливо ГМЛ, після ядерного бомбування, зберігався впродовж усього 55–річного періоду спостереження [7]

Результати дослідження лейкемії свідчать про наявність нелінійної відповіді на дозу (окрім ХЛЛ та Т–клітинної лейкемії дорослих), яка помітно коливалась, залежно від віку на момент експозиції та збіглого часу після неї. Надлишковий ризик лейкемії, як правило, знижувався з досягненням більш похилого віку чи з часом після опромінення [7].

Ризики хронічної ХЛЛ не аналізувались, оскільки така патологія надзвичайно рідкісна в популяції Японії, і вона майже не реєструвалась серед радіаційно–зумовлених захворювань. Хоча в публікації [7] наводяться перші висновки щодо ймовірного етіологічного звязку ризику виникнення ХЛЛ із опроміненням, які базувались лише на 7 випадках ХЛЛ, ідентифікованих в когорті хібакуші.

Надлишок виникнення солідних пухлин було визначено в категоріях пожиттєвого дозо залежного ризику [3]. Оцінки визначались для специфічної статі і віку на момент опромінення. Надлишок пожиттєвого ризику на 1 Зіверт опромінення у віці 30 років для солідних пухлин було оцінено на рівні 0,10 і 0,14 для чоловіків і жінок відповідно. Для опромінених у віці 50 років – величина ризику була на третину меншою від вище названих. Прогноз для опромінених у віці 10 років менш визначений, але його значення припускається на рівні приблизно 1,0–1,8 такого, що визначений для віку 30 років. Пожиттєвий ризик лейкемії на 1 Зіверт опромінення для осіб, опромінених у віці 10 або 30 років оцінюється в приблизно 0,015 і 0,008 для чоловіків і жінок відповідно. Для тих, хто опромінений у віці 50 років, оцінка ризику становить приблизно дві третини від цих рівнів [2].

Отримані оцінки було уточнено на останньому етапі аналізу даних дослідження впродовж життя (LSS) за період 1958–2009 рр. [8] Надлишковий ризик було оцінено із розрахунку віку 30 років на момент експозиції і 70 років досягнутого віку. Аналіз базувався на 22 538 нових випадках злоякісних новоутворень, з числа яких 992 було визначено як радіаційно зумовлені, та 3079 484 людино–роках спостереження. Для жінок було визначено, що доза-відповідь була лінійною з ERR на рівні 0,64/Gy (95% ДІ: 0,52 до 0,77). Для чоловіків спостерігалось статистично значуще викривлення вгору як за весь діапазон доз, так і в окремих дозових інтервалах. У звязку з цим, надлишок ризиків було розраховано за лінійно–квадратичною моделлю на рівні ERR=0,20 (95% ДІ: 0,12–0,28) на

1 Гр і ERR=0,010 (95% ДІ: -0,0003–0,021) на 0,1 Gy опромінення. Крива доза–відповідь у жінок суттєво відрізнялась від такої у чоловіків (p=0,02)). Найнижчі значення доз, для яких було визначено суттєвий рівень доза–відповідь з використанням усередненої для обох статей лінійної ERR–моделі, був діапазон 0–100 мГр (p = 0.038).

Ці оцінки, отримані для осіб, опромінених, переважно, майже одномоментно у високих дозах зовнішнього опромінення, в подальшому, лягли в основу прогнозних оцінок онкологічних наслідків в інших опромінених популяціях. Дослідження впливу тривалого або фракційного опромінення у малих чи великих дозах не втрачають актуальності і досі.

Опромінення широких верств населення в різних діапазонах доз спостерігається як від природніх джерел (космічна енергія, експозиція до натуральних радіонуклідів у повітрі, воді і грунті, так і із штучно генерованих джерел (виробництво атомної електричної енергії, видобуток радіаційно місткої руди для промислових потреб, використання технічних засобів і медичних препаратів для рентгенівської та радіонуклідної діагностики і лікування, тестування озброєння) [9, 10]. Підвищені ризики онкологічних захворювань спостерігались серед осіб, залучених у використання цих джерел як у штатному режимі, так і в аварійних ситуаціях.

Надлишковий ризик виникнення злоякісних новоутворень внаслідок аварійного опромінення визначено у 21 500 працівників (25 % з них – жіночої статі) ядерного виробничого комплексу «Маяк», розташованого в Російській Федерації, які пролонговано отримали значну дозу зовнішнього опромінення (у середньому 0,8 Гр) в період між 1948 і 1972 роками [11, 12]. Стан здоров’я кожного працівника простежувався з початку його роботи на підприємствах комплексу до 1997 р., в середньому, 40 років. Було встановлено статистично значущий дозо залежний ексцес смертності від лейкемії. Була визначена достовірна залежність величини надмірного ризику лейкемії від періоду отримання дози. Для доз,

отриманих за період від 3 до 5 років до смерті, ексцес відносного ризику склав приблизно 7 на 1 Гр опромінення ($p < 0,001$), але такий показник становив лише 0,45 на 1 Гр ($p = 0,02$) для доз, отриманих за час від 5 до 45 років до смерті за рахунок зовнішнього гамма-випромінювання [11]. Для солідних раків в цілому надлишок відносного ризику для зовнішнього опромінення із урахуванням опромінення від ^{239}Pu за лінійною моделлю доза–відповідь склав 0,15 (90 % CI: 0,09, 0,20). Додавання в модель квадратичного компоненту збільшувала оцінку вдвічі до рівня ERR* Gy^{-1} = 0,30 (90% CI: 0,18, 0,43). Оцінки ризиків для працівників виробничого комплексу дещо нижчі від таких, отриманих для когорти LSS, але будь-які порівняння мають враховувати суттєві невизначеності доз для когорти виробництва «Маяк» [12]. Навіть після врахування експозиції до плутонію, оцінки ризиків для зовнішнього гамма опромінення разом для раку легені, печінки та кості перевищують оцінки для всіх інших форм раку. Це пов'язано із технічними складностями врахування дози від плутонію. Лінійна оцінка ERR*Gy^{-1}, із урахуванням впливу від плутонія, була 30 (90% CI: 0,18, 0,46) Gy^{-1} для легені, печінки та кості, і 0,08 (90% CI: 0,03, 0,14) Gy^{-1} для інших солідник раків.

Впливу радіації у зв'язку із функціонуванням виробничого комплексу, крім працівників, зазнали мешканці прилеглих територій. Провендено аналіз захворюваності на злоякісні новоутворення в когорті осіб, які мешкали на території Східно–Уральського радіоактивного сліду (21 394 особи), який утворився після вибуху резервуару у сховищі радіоактивних відходів у 1957 р. та опадів радіоактивної хмари на прилеглі території [13]. Надлишковий відносний ризик захворюваності на солідні пухлини в цій когорті склав ERR=0,049/100мГр (90% ДІ:0,003; 0,10; p=0,077), а з вилученням із аналізу 55 випадків ЗН товстого кишківника і 3 випадків ЗН кісток (у звязку із суттєвою відмінністю оцінок доз опромінення на ці органи від інших органів) ERR/100 мГр склав 0,054 (90% 0,007; 0,107; p=0,06). Ці результати подібні до таких для когорти

річки Теча, в яку протягом багатьох років потрапляли відходи виробництва «Маяк» (ERR/100 мГр=0,08; 95% ДІ:0,01;0,15) [11, 14]. Останні дослідження показали, що величина ризика виникнення солідних пухлин на одиницю дози при хронічному опроміненні в діапазоні малих або середніх доз, може бути відповідною до такої при високих дозах.

Найбільшою техногенною радіаційною аварією сучасності стала аварія на Чорнобильській АЕС в 1986 р. Близько 200 000 km^2 території в Європі були забруднені радіонуклідами щільністю понад 37 kBq/m^2 за ^{137}Cs. • Приблизно $14x10^{18}$ Bq радіоактивності було викинуто в атмосферу переважно за рахунок ^{131}I and ^{137}Cs. 115 000 мешканців було евакуйовано в 1986 р. і ще понад 220 000 мешканців України, Білорусі, Росії було переселено пізніше [10, 15]. Найближчим часом після аварії прийшло розуміння того, що потенційні спричинені нею медичні і екологічні проблеми, виходять за рамки локальних [15, 16, 17].

Потенційні загрози спонукали міжнародні інституції вести постійний моніторинг ситуації на прилеглих до станції територіях, в групах населення, евакуйованого із зон впливу і задіяного в аварійні та ліквідаційні роботи. Паралельно в трьох постраждалих країнах (в минулому – радянських республіках) за фінансової та методологічної підтримки міжнародних інституцій (ВООЗ, НКДАР, МКРЗ ООН) виконувались багаторічні програми з гуманітарної допомоги устаткуванням, засобами і методиками дозиметричного, лабораторного і клінічного, моніторингу поточного стану постраждалих, а також дослідження медичних наслідків аварії в групах задіяного населення (IPHECA, SASAKAWA та ін.) [18, 19].

Результати проектів, реалізованих впродовж після аварійних 10 років, за участі міжнародних організацій, було представлено експертами на підсумковій конференції «Десять років після Чорнобилю: підсумки наслідків аварії», яка відбулась у Відні 8–12 квітня 1996р.

Представлені етапні висновки міжнародних експертів констатували причинно–наслідковий зв'язок між опроміненням в молодшому дитячому віці і надлишком випадків РЩЗ. Таким оцінкам сприяли визначені територіально–часові характеристики виникнення випадків. У висновках експертів було також підкреслено, що опубліковані на той час дані описових епідеміологічних досліджень в Україні, Білорусі та Росії, які свідчили про суттєве зростання захворюваності на інші злоякісні новоутворення в когортах постраждалого населення (мешканців радіоактивно забруднених територій і учасників ліквідації насідків аварії), не є достатньо обґрунтованими [20]. Крім того, методи ідентифікації випадків не викликали довіри, тому наголошувалось на необхідності проведення аналітичних епідеміологічних досліджень в цих групах постраждалих, які стануть джерелом ґрунтовних висновків.

Згідно з експертними оцінками [20], для учасників ліквідації наслідків аварії в 1986–1987 рр прогнозна оцінка атрибутивної фракції кількості випадків смерті від солідних пухлин впродовж життя (до віку 95 років включно), пов’язаних із опроміненням після аварії, склала приблизно 5%. В той же час, для лейкемії цей рівень оцінювався на рівні 20 % із максимальною реалізацією в перші 10 років. В той же час, ідентифікація збільшеного числа випадків захворювань, згідно з експертними оцінками, може бути спричиненою особливим рівнем медичного обслуговування опромінених контингентів населення.

Подібні за суттю були висновки за результатами досліджень впродовж 20 років, які сплили після катастрофи, і протягом яких продовжувались національні програми моніторингу випадків злоякісних новоутворень в групах постраждалих осіб. В 2006 р. було опубліковано науковий звіт під егідою восьми міжнародних інституцій, задіяних у дослідження і вирішення Чорнобильських проблем впродовж всіх років після аварії (Європейська комісія, МАГАТЕ, ВООЗ, НКДАР, Програма розвитку ООН та інші), пов’язаних із Чорнобильською аварією [21, 22], в

якому проаналізовано наявні на той час відомості про реалізовані ризики, визначено необхідність проведення доказових аналітичних епідеміологічних досліджень. У звіті підкреслено, що популяційною групою, в якій можливо дослідити радіаційно зумовлений надлишок захворюваності на злоякісні новоутворення, якщо він взагалі існує у зв'язку із опроміненням після аварії на ЧАЕС, є учасники ЛНА. Це зумовлено порівняно високим середнім рівнем опромінення і, звідси, надлишковою кількістю захворювань, яку можливо виділити із числа спонтанних випадків, характерних для популяційної групи таких розміру і статево–вікової структури. Дози учасників ЛНА з України оцінювались, в середньому 151 мЗв для зовнішнього опромінення, в тому числі приблизно 186 мЗв для учасників 1986 р., 127 мЗв – 1987 р., 57 мзв – 1988 р., та приблизно 50 мЗв – 1989–1990 рр. [10].

Альтернативний звіт (TORCH), у відповідь на офіційно опублікований звіт міжнародних інституцій щодо екологічних і медичних наслідків аварії на ЧАЕС впродовж 20 років, що зійшли після аварії, було ініційовано організацією European greens (Європейські зелені). В ньому було констатовано на порядок вищі рівні забруднення довкілля радіонуклідами і, як наслідок, прогнозовано на порядок більшу кількість випадків раку, індукованих в результаті надлишкового опромінення. Такі оцінки були зроблені як для пострадянських республік, так і для європейських країн в цілому.

В той же час, моніторинг випадків злоякісних новоутворень, діагностованих в групах опромінених осіб, не припинявся в наукових і медичних установах трьох пострадянських республік, які найбільше постраждали від аварії на ЧАЕС [23–28]. За даними цих досліджень, в Україні було визначено, що показники захворюваності на всі форми раку перевищують національний рівень тільки в групі УЛНА 1986–1987 рр. В трьох основних групах постраждалих виявлено істотний ріст захворюваності на рак щитоподібної залози, що може бути зумовлено

опроміненням цього органу за рахунок випадінь радіоактивного йоду. Зростання частоти цієї патології під впливом радіаційного опромінення встановлено не тільки у дітей, а також у підлітків і дорослих. Аналіз захворюваності на рак щитоподібної залози різних груп постраждалого населення показав найбільш значне перевищення національного рівня в УЛНА 1986–1987 рр. – в 4,8 раза, евакуйованих – в 4,1 раза, жителів найбільш забруднених радіонуклідами територій – в 1,3 раза [25, 27]. Також викликало занепокоєння зростання захворюваності на рак молочної залози серед учасниць ліквідації наслідків аварії та серед населення контрольованих територій жіночої статі [24, 25, 29]. Окремими дослідженнями було визначено підвищену захворюваність на лейкемію серед дітей, які мешкали на забруднених радіонуклідами територіях [28].

Дослідження загальної популяції, що зазнала впливу ^{131}I після аварії на ЧАЕС, показало значний ексцес РЩЗ після опромінення в дитячому віці, який був значно вищим, ніж очікувався [26]. Дані про тих, хто був експонований у дорослому віці, є більш суперечливими.

Результатам, отриманим в Україні, відповідають дані досліджень серед російських УЛНА. Аналіз SIR в когорті російських ліквідаторів впродовж 1992–2009 рр.. показав статистично значуще збільшення захворюваності на рак у досліджуваній когорті, порівняно зі спонтанним рівнем захворюваності на цю патологію серед чоловіків Росії. Показники захворюваності на солідні ЗН за період 1992–2012 рр. серед російських УЛНА дещо знизились і, в середньому, на 11 % перевищували відповідні показники чоловічого населення Росії. SIR спостерігалось на рівні 1,11 (95 % ДІ: 1,09–1,14) [30].

За результатами національних описових і екологічних досліджень в когортах УЛНА вироблялись гіпотези для планування і проведення аналітичних епідеміологічних досліджень, реалізованих пізніше за участі міжнародних наукових інституцій.

У низці техногенних аварій сучасності із надмірним радіаційним опроміненням сотень тисяч цивільних осіб, поряд із Чорнобильською аварією, розглядаються наслідки аварії на атомній електростанції Фукусіма–Даічі (FDNPS), яка трапилась 11 березня 2011 р. після дев'ятибального землетрусу і викликаної ним цунамі [31]. Загальна кількість радіоактивних матеріалів, яка потрапила в атмосферу, дорівнювала 9–37 pBq за ^{137}Cs, а прямі викиди в океан склали 3–6 pBq, число евакуйованих і переміщених осіб в префектурі Фукусіма в 2012 р. склало 160 000 осіб. 25 000 осіб брали участь в аварійних та роботах з ліквідації наслідків аварії. Більшість цих осіб (99.3 %) отримала дози опромінення менші за 100 мЗв, в середньому близько до 10 мЗв, і тільки 173 працівника, згідно з оцінками, отримали ефективні дози, більші за 100 мЗв (в середньому, близько 140 мЗв), переважно за рахунок зовнішнього опромінення. Оцінки ризику для працівників відповідають приблизно двом–трьом випадкам раку додатково до приблизно сімдесяти випадків раку, які можуть виникнути спонтанно. Таке підвищення може бути складно вивити і пов'язати із опроміненням внаслідок відсутності специфічних маркерів, а також за підвищеного рівня медичного обстеження цих контингентів.

Поряд із випадками позаштатного опромінення в аварійних ситуаціях, сотні тисяч працівників зазнають опромінення в різних дозах, зумовленого характером професійної діяльності. Перш за все, йде мова про працівників атомних електричних станцій, медичних радіологів, працівників підприємств із видобування та обробки руди із вмістом радіоактивних сполук. Стан здоров'я осіб, залучених у такі роботи, контролюється і досліджується для розробки нових стандартів при роботі із джерелами іонізуючого випромінювання

Усі попередні дослідження, окремі та об'єднані, виявляють позитивний зв'язок між смертністю від лейкемії, виключаючи ХЛЛ, та професійним впливом іонізуючого випромінювання. Оцінки надлишкового

відносного ризику лейкемії (без ХЛЛ) в когортах працівників з Франції [32], Великобританії [33] та США [34] складають: 3,96 (90% ДІ: <0,0, 16,82), 1,71 (90% ДІ: 0,06, 4,29) та 1,7 (95% ДІ: -0,22, 4,7) відповідно. У дослідженні працівникіів АЕС 15 країн оцінка ризику становила 1,93 (95% ДІ: <0,00, 8,47) [35].

Дослідження INWORKS, включивши значну кількість додаткових років спостереження, порівняно з попередніми об’єднаними міжнародними дослідженнями, значно збільшило статистичну потужність і, звідси, точність оцінок наслідків низькорівневого хронічного впливу іонізуючого випромінювання. До дослідження INWORKS в об’єднаній когорті працівників атомних станцій США, Франції і Великобританії увійшли 308 297 осіб [36]. На відміну від типових когортних професійних досліджень, усі працівники, включені до INWORKS, мають записи, які надають індивідуальні кількісні оцінки дози опромінення. Працівники, включені до INWORKS, в основному, зазнавали впливу зовнішнього гамма-випромінювання, а дози регулярно вимірювали за допомогою особистих дозиметрів. Для всіх когорт-учасників облік окремих зареєстрованих доз ведеться з самого початку промисловості в 1940-х роках.

На сьогоднішній день, основні висновки INWORKS включають аналіз асоціації між радіацією та лейкемією і лімфомою. Надлишковий відносний рівень смертності від лейкемії (без ХЛЛ) склав 2,96 (90% ДІ: 1,17, 5,21) на 1 Гр опромінення червоного кісткового мозку [37].

Як і в будь-якій об'єднаній когорті, в INWORKS існує ряд обмежень. Для всіх членів когорти неможливо отримати додаткову інформацію щодо потенційних змішуючих факторів (confounding factors), включаючи куріння або інші впливи, які можуть модифікувати оцінки, а також не виключеним є єфект здорового працівника [38].

Оцінки щодо ефектів радіаційного впливу були також отримані за результатами досліджень в групах осіб, які були опромінені за медико-діагностичними або терапевтичними потребами [39–42]. Поширене

використання новітнього рентгенологічного та іншого променевого устаткування в медицині пов’язано із надлишковим виникненням злоякісних новоутворень, яке має ймовірнісний характер, залежить від отриманої дози, характеру опромінення і індивідуального сприйняття опромінення організмом. Тому в наш час постійно виконуються дослідження рівнів і пов’язаних з ними ефектів опромінення з медичною метою, щоб, як і в інших випадках, оцінити можливість, необхідність і нормативи використання з урахуванням відносної шкали користь-шкода.

У зв’язку із поширеним використанням іонізуючого випромінювання у виробничих і медичних цілях, зростає ймовірність аварійних ситуацій, які можуть призвести до несанкціонованого опромінення осіб, задіяних у такому професійному циклі, а також медичних працівників і пацієнтів. Тому оцінки ризиків стохастичних ефектів опромінення в результаті ретельно спланованих і реалізованих аналітичних досліджень мають суттєве не тільки теоретичне, але і практичне значення для обмеження негативного впливу і мінімізації можливих наслідків несанкціонованого опромінення в широкому діапазоні доз.

Підсумовуючи наведені публікації, слід вказати на те, що накопичена на сьогодні інформація свідчить про суттєву роль радіаційного фактору у формуванні надлишку виникнення злоякісних новоутворень в цілому та їхніх окремих нозологічних форм в опромінених популяціях. Досвід проведення аналітичних досліджень було проаналізовано і використано для розробки методології проведення таких досліджень в Україні з метою ґрунтовної оцінки медичних наслідків аварії на ЧАЕС в Україні. Такі дані також допоможуть у розробці критеріїв і нормативів використання джерел іонізуючого випромінювання із соціально прийнятними рівнями ризиків, пов’язаних із цим

Актуальність дослідження, таким чином, обумовлена необхідністю достовірної та науково обгрунтованої кількісної оцінки

стохастичних віддалених біологічних ефектів пролонгованого опромінення людини малими та середніми дозами іонізуючого випромінювання

Зв'язок роботи з науковими програмами, планами, темами.

Дисертаційна робота виконана в Інституті радіаційної гігієни і епідеміології ННЦРМ НАМН України і відповідає основним напрямкам наукової діяльності Інституту. Гудзенко Н.А. була відповідальним виконавцем науково–дослідних робіт, які:

- виконувались за науковим планом НАМН в лабораторії сполучних та комбінованих ефектів радіації, пізніше – в лабораторії епідеміології раку, а саме:

«Провести верифікацію випадків лейкемій в учасників ліквідації наслідків аварії на ЧАЕС в Державному та спеціалізованих реєстрах.»,

(№ держреєстрації 0102U005687), 2002–2004 рр.»;

«Дослідження лейкемій та споріднених захворювань серед учасників ліквідації наслідків аварії на Чорнобильській АЕС»

№ держреєстрації 0304U001727, 2005–2009 рр.;

«Проаналізувати якість інформаційної системи медичного моніторингу в "Державному реєстрі України осіб, які постраждали внаслідок Чорнобильської катастрофи»

(№ держреєстрації 0104U003637), 2004–2006 рр.»;

«Визначити закономірності формування захворюваності на злоякісні новоутворення основних груп населення, яке постраждало внаслідок аварії на ЧАЕС, на довгостроковому етапі епідеміологічного моніторингу»

(№ держреєстрації 0107U000909), 2007–2009 рр.

«Визначити закономірності формування радіаційно асоційованих онкологічних ризиків у населення, яке постраждало внаслідок Чорнобильської катастрофи, у віддалений після аварійний період»

№ держреєстрації 0107U000909, 2010–2012 рр;

«Дослідити еволюцію захворюваності на злоякісні новоутворення у постраждалих внаслідок Чорнобильської катастрофи за результатами 25-річного епідеміологічного моніторингу»,

№ держреєстрації 0113U002319, 2013–2015 рр.,

«Дослідження внеску радіаційного фактору у формування захворюваності на злоякісні новоутворення окремих груп постраждалих внаслідок аварії на Чорнобильській АЕС за результатами 30–річного періоду спостереження»

№ держреєстрації 0116U002478, 2016–2018 рр.

«Епідеміологічне дослідження формування ризиків злоякісних новоутворень у групах постраждалих внаслідок аварії на ЧАЕС (1990–2019 рр.)»

№ держреєстрації 0119U100525, 2019–2021 рр.;

- за міжгалузевою комплексною програмою «Здоров'я нації» "Розробити систему взаємодії спеціалізованих популяційних реєстрів України різного профілю для удосконалення моніторингу злоякісних новоутворень", № держреєстрації 0107U000929), 2007–2009 рр..

Була співвиконавцем пректу за Німецько-Французькою ініціативою "Чорнобиль" (1999–2001 рр.); була керівником епідеміологічної групи в проектах, що фінансувались Національним інститутом раку США, а саме: «Спільне американо-українське дослідження лейкемії та інших гематологічних захворювань серед учасників ліквідації наслідків аварії на ЧАЕС в Україні», (1998–2009); «Спільне американо-українське дослідження раку щитоподібної залози серед учасників ліквідації наслідків аварії на ЧАЕС в Україні» (2010–2015); «Спільне американо-українське дослідження генетичних ефектів опромінення серед учасників ліквідації наслідків аварії на ЧАЕС в Україні та їхніх нащадків (ТРІО)" (2015–2021).

Метою роботи було розробити та практично застосувати комплексну методологію аналітичного епідеміологічного дослідження стохастичних медико-біологічних ефектів іонізуючого випромінювання в

Україні та визначити на її основі ризики виникнення віддалених онкологічних і генетичних ушкоджень внаслідок опромінення під час ліквідації наслідків Чорнобильської катастрофи.

Для досягнення мети були сформульовані та **розв'язані наступні наукові задачі:**

1. Обгрунтувати необхідність аналітичних епідеміологічних досліджень для оцінки ризиків стохастичних ефектів опромінення внаслідок участі в ліквідації наслідків аварії.
2. Визначити складові реалізації аналітичного епідеміологічного дослідження, які забезпечують доказовість його висновків.
3. Оцінити інформативність та можливість використання національних популяційних реєстрів України для формування і простеження когорти учасників ліквідації наслідків аварії на ЧАЕС та ідентифікації випадків досліджуваних захворювань.
4. Розробити технологію визначення випадківдосліджуваних захворювань і верифікації діагнозів..
5. Розробити технологію пошуку суб'єктів дослідження, встановлення з ними контакту та проведення анкетування з урахуванням принципів медичної етики.
6. Обгрунтувати епідеміологічні критерії вибору методів дозиметрії для використання в аналітичному епідеміологічному дослідженні стохастичних ефектів опроміннення.
7. Сформувати інформаційну базу для проведення аналізу ризиків лейкемії в досліджуваній когорті та провести ретроспективне епідеміологічне дослідження лейкемії та РЩЗ серед УЛНА.
8. Оцінити реалізовані ризики лейкемії і раку щитоподібної залози в досліджуваній когорті з урахуванням впливу радіаційного та інших чинників.
9. Дослідити можливі дозо-залежні особливості реалізації випадків хронічної лімфоцитарної лейкемії,

10. Визначити наявність дозозалежних генетичних ушкоджень у учасників ліквідації наслідків аварії, які могли передатись їхнім нащадкам.

Об'єкт дослідження: віддалені стохастичні ефекти опромінення серед учасників ЛНА на ЧАЕС в Україні та їхніх нащадків.

Предмет дослідження:

методи здійснення аналітичних епідеміологічних досліджень реалізації стохастичних ефектів опромінення, спричиненого участю у ліквідації наслідків аварії на ЧАЕС;

ризики виникнення стохастичних ефектів (лейкемії, раку щитовидної залози, мутацій de novo в нащадків опромінених батьків) внаслідок дії іонізуючого випромінювання на людину під час участі в ЛНА ЧАЕС;

вплив модифікуючих факторів на результати ризик–аналізу.

Методи дослідження: соціологічні (пошук та опитування суб'єктів дослідження), статистичні (розрахунок статистичної потужності, оцінка достовірності результатів), епідеміологічні (визначення дизайну дослідження, методів контролю якості даних, оцінка коефіцієнтів ризику).

Актуальність дослідження обумовлена необхідністю достовірної та науково обґрунтованої кількісної оцінки стохастичних віддалених біологічних ефектів пролонгованого опромінення людини малими та середніми дозами іонізуючого випромінювання.

Наукова новизна одержаних результатів полягає в тому, що:

- Вперше було визначено, методично опрацьовано і впроваджено на практиці основні складові аналітичного епідеміологічного дослідження в Україні, які забезпечують якість оцінок ризиків стохастичних ефектів опромінення, зокрема:.
    - науково обґрунтовано вибір дизайну епідеміологічного дослідження стохастичних ефектів опромінення в Україні, критерії формування когорти із необхідним обсягом

індивідуальних даних і визначеним періодом спостереження для забезпечення прийнятної потужності дослідження;

- розроблено комплексну методику визначення випадків досліджуваних захворювань в повному обсязі із забезпеченням верифікації діагнозів для подальшого включення до аналізу ризиків;
- обгрунтовано епідеміологічні критерії вибору методів реконструкції індивідуальних доз опромінення і визначено способи забезпечення необхідними даними.

- На основі розроблених методичних засад вперше було визначено ризики виникнення стохастичних ефектів опромінення серед ліквідаторів в Україні, а саме:
  - вперше серед учасників ліквідації наслідків аварії на ЧАЕС в Україні було визначено достовірну лінійну позитивну асоціацію між кумулятивною дозою опромінення на червоний кістковий мозок з надлишком відносного ризику виникнення лейкемії на 1 Грей опромінення (ERR/Gy), який протягом 1986 – 2000 рр склав 3.44 (95 % довірчий інтервал: 0.47–9.78, p<0,01), а впродовж1986–2006 рр. – 2,38 з 95 % ДІ від 0,49 до 5,87 та p=0,004;
  - вперше було визначено позитивну дозо залежну асоціацію ризиків виникнення хронічної лімфоцитарної лейкемії впродовж 1986–2006 рр. серед ліквідаторів в Україні (ERR/Gy=2,58, 95% довірчий інтервал 0,02–8,43 і p=0,047);
  - вперше було визначено суттєвий вплив професійного контакту із бензином на надмірний ризик виникнення мієлоїдної лейкемії, переважно, за рахунок її хронічної форми. Співвідношення шансів (OR) склало 3,48, 95% довірчий інтервал: 1,09–11,12.

- перші висновки аналітичного дослідження свідчать про збільшення ризику раку ЩЗ серед УЛНА на ЧАЕС, хоча із статистично граничною значущістю (надлишок відносного ризику (ERR/Gy)=0.40; 95% довірчий інтервал: -0.05, 1.48; p=0.12);
- вперше, за результатами генетичного дослідження учасників ліквідації наслідків аварії на ЧАЕС і їхніх нащадків в Україні, було доведено відсутність но поточний момент дозозалежних спадкових генетичних ушкоджень у дітей, народжених від батьків, опромінених внаслідок участі в ЛНА на ЧАЕС або в процесі евакуації.

Практична значущість одержаних результатів полягає в тому, що оцінки радіаційних ризиків в національній популяції учасників ліквідації наслідків аварії на Чорнобильській АЕС є репрезентативними для населення виробничо і соціально активного віку, збагатять світову науку новими знаннями про ризики виникнення радіоіндукованих віддалених ефектів та можуть бути використані в розробці критеріїв безпеки та допустимих рівнів професійного опромінення. Позаяк медичне опромінення набуває все більших масштабів в Україні і у світі в цілому, визначення коефіцієнтів ризиків також сприятиме покращенню радіаційного захисту медичного персоналу та пацієнтів.

На основі результатів роботи, у співпраці із співробітниками лабораторії епідеміології раку ННЦРМ, відділу гематології ННЦРМ, Національного канцер–реєстру України було розроблено методичні рекомендації з проведення контролю якості інформації на різних рівнях функціонування ДРУ, Київ, 2007; з технології інформаційної взаємодії ДРУ та НКРУ, Київ, 2010; стосовно алгоритму альтернативних розрахунків розміру досліджуваної когорти в динаміці спостереження, на прикладі даних ДРУ, Київ, 2011. Крім того, була видана відомча інструкція

«Алгоритм верифікації злоякісних захворювань кровотворної та лімфоїдної систем у учасників ліквідації наслідків аварії на ЧАЕС», Київ, 2006.

Матеріали дисертаційної роботи було використано при підготовці Національних доповідей України: 25 років Чорнобильської катастрофи. Безпека майбутнього : Національна доповідь України, 2011, (розділ 3.2.1), «Тридцять років Чорнобильської катастрофи: радіологічні та медичні наслідки» Національна доповідь України , 2016 р. (розділи 2.7 і 2.8) і “Тридцять пять років Чорнобильської катастрофи: радіологічні та медичні наслідки, стратегії захисту та відродження», 2021 (розділи 2.2; 2.3.; 2.4; 3.5);

Особистий внесок здобувача

Наукові статті, в яких представлені основні результати дисертаційної роботи, написані у співавторстві. Всі основні результати одержані автором особисто або за його безпосередньої участі в співпраці із колегами із Національного наукового центру радіаційної медицини НАМН України, Національного інституту раку США (Бетезда, США), Колумбійського університету (Нью Йорк, США). Дисертант приймав активну участь у виборі та обґрунтуванні напрямів досліджень, постановці конкретних завдань, у визначенні критеріїв формування когорти і досліджуваних груп в когорті, джерел і способів ідентифікації випадків, інформаційному забезпеченні міжнародної діагностичної експертизи, в аналітичному етапі досліджень (формування аналітичної бази даних, аналіз ризиків). Йому належить провідна роль у проведенні аналізу впливу потенційних модифікуючих чинників на оцінки дозозалежних ризиків виникнення лейкемії. Дисертант брав активну участь в інтерпретації всіх отриманих результатів, у плануванні, підготовці і написанні всіх опублікованих статей, тез та доповідей конференцій. Таким чином, особистий внесок дисертанта в даній роботі є визначальним.

Апробація результатів дисертації. Результати та висновки дисертаційної роботи доповідались та обговорювались на: III Междунар. симпозиумі «Хроническое радиационное воздействие: медико-биологические эффекты» Челябинск, 24 – 26 октября 2005; Гематологія і трансфузіологія: фундаментальні та прикладні питання: наук.–практ. конф., Київ, 13-14 жовтня 2005 р; the 21st International CODATA Conference, Kyiv, Oct. 5–8, 2008; Міжнародна наук.–практ. конф. з питань соціального захисту громадян, які постраждали внаслідок Чорнобильської катастрофи. 24–25 квітня 2008 року; VI съезд онкологов и радиологов стран СНГ, Душанбе, 1−4 окт. 2010; XIII конгрес світової федерації українських лікарських товариств ,Львів, 01–03 жовт. 2010 р.; Радіобіологічні та радіоекологічні аспекти Чорнобильської катастрофи: міжнародна конференція, Славутич, 11–15 квітня 2011; 14th International Congress of Radiation Research, The Chernobyl impact on health and environment: Satellite Symposium, Kyiv, 2–3 September 2011; Другий Всеукраїнський конгрес з медичного права, біоетики і соціальної політики, Київ, 14–15 квітня 2011; XII з'їзд онкологів України, Судак, 20–22 вересня 2011 р; Двадцять п'ять років Чорнобильської катастрофи. Безпека майбутнього: Міжнародна наук.-практ. конф. Київ, 20–22 квітня 2011; XV з'їзд гігієністів України 20–21 вересня Львів, 2012; ASA Conference on Radiation and Health, June, 10-13, 2012 .Kennebunkport,ME, «Радіоекологія-2014», м. Київ, 23–26 квітня, 2014, «Актуальні питання гігієни та екологічної безпеки України», Київ 9–10 жовтня 2014; Міжнародна наук. конф. «Радіологічні та медичні наслідки Чорнобильської катастрофи – 30 років по тому», Київ 18–19 квітня 2016 р.; науч. –практ. конф. п'ятнадцяті (17–18 жовтня 2019 р), шістнадцяті (12–13 листопада 2020 р.) Марзєєвські читання;. 12th congress of the European Hematology Association, Madrid, 2019; conference of the International Society for Environmental Epidemiology **(ISEE 2019)** Utrecht, the Netherlands, 25–28, August, 2019; 7-й з'їзд

радіобіологічного товариства України. Київ, 1–4 жовтня 2019; XVI міжнародна наук.-практ. конф. (XVI RADTES–2020)

Публікації. За темою дисертації опубліковано 23 роботи, в т.ч. 15 наукових праць у виданнях, які належать до першого та другого квартилів (Q1 і Q2), відповідно до класифікації SCImago Journal and Country Rank або Journal Citation Reports, 8 статей у інших фахових виданнях, 22 тез доповідей на конференціях, видано 3 методичні рекомендації, 1 відомча інструкція.

Відповідно до восьмого абзацу підпункту 1 пункту 2 Наказу МОН України "Про опублікування результатів дисертацій на здобуття наукових ступенів доктора і кандидата наук" від 23.09.2019 р. № 1220 та враховуючи наявність трьох публікацій в одному номері журналу ([5], [6] та [7]), еквівалентна кількість публікацій, у яких відображені основні наукові результати, прирівнюється до 51 публікації.

Структура та обсяг дисертації. Дисертація підготовлена у вигляді наукової доповіді. Робота складається із анотації, основної частини, та додатку. До основної частини дисертації включено 16 статей у фахових наукових виданнях, які згруповані у 8 розділів. Загальний обсяг дисертації 259 сторінок, обсяг основної частини – 213 сторінок.

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1. СТАН ПРОБЛЕМИ: РЕЗУЛЬТАТИ ДЕСКРИПТИВНИХ ДОСЛІДЖЕНЬ СЕРЕД УЧАСНИКІВ ЛІКВІДАЦІЇ НАСЛІДКІВ АВАРІЇ НА ЧАЕС І В ІНШИХ ГРУПАХ ПОСТРАЖДАЛИХ ОСІБ. ОБГРУНТУВАННЯ АНАЛІТИЧНИХ ЕПІДЕМІОЛОГІЧНИХ ДОСЛІДЖЕНЬ

Перші епідеміологічні дослідження, ініційовані і проведені серед населення України після аварії на ЧАЕС, носили дескриптивний характер, мали у звязку з цим суттєві обмеження, але сигналізували про проблеми для обов'язкового моніторингу і дослідження.

В трьох основних групах постраждалих було виявлено істотний ріст захворюваності на рак щитоподібної залози, що могло бути зумовлено зовнішнім опроміненням цього органу та внутрішньою експозицією за рахунок потрапляння в організм випадінь радіоактивного йоду з їжею і водою.

В **підрозділі 1.1** надається характеристика захворюваності на РЩЗ в групах постраждалих осіб. Серед учасників ліквідації наслідків аварії на ЧАЕС 1986-1987 рр визначений рівень перевищував такий для населення України— в 5.9 рази (1994-2006), серед евакуйованих – в 5.4 рази (1994-2006 рр), серед мешканців забруднених радіонуклідами територій – в 1.5 раз (1990-2006)

В **підрозділі 1.2** представлено результати екологічного дослідження з порівняльним аналізом захворюваності на рак щитовидної залози в Україні після аварії на Чорнобильській АЕС у когорті, яка за розміром майже відповідала загальній популяції України. Порівнювались території, умовно визначені як « з високою експозицією» і з «низькою експозицією». Критерієм розподілу була кумулятивна доза опромінення, реконструйована для осіб 0-18 років на момент аварії. Території визначались як з високою експозицією, якщо кумулятивна доза

опромінення китоподібної залози перевищувала 35 мГр. Результати цього дослідження, підтвердили високу вразливість молодших вікових груп до радіаційного онкогенезу. Особливо чутливою була наймолодша вікова група, яка складалась із осіб, народжених у 1982–1986 роках, тобто у віці 0–4 років на момент аварії на Чорнобильській АЕС.

Підрозділ 1.3 присвячений узагальненню висновків міжнародної експертної групи (Чорнобильський форум), створеної в 2003 р, під егідою Європейська комісія та міжнародних інституцій ООН (МАГАТЕ, ВООЗ, Програма розвитку ООН), до складу якої входила і дисертант. Міжнародними експертами результати описових досліджень наслідків аварії, наявні на той час, були визначені недостатньо обґрунтованими і такими, що потребували підтвердження в адекватно спланованих і проведених дослідженнях аналітичного характеру.

Узагальнені висновки Чорнобильського форуму полягали у відсутності підтверджених доказів ефектів аварії на Чорнобильській АЕС щодо лейкемії, РЩЗ та інших форм раку в групах опромінених осіб, в тому числі серед учасників ЛНА. Єдиним доведеним медичним ефектом аварії було визнано РЩЗ серед опромінених мешканців найбільш забруднених радіонуклідами територій наймолодшої вікової групи.

Разом з тим, для отримання обгрунтованих висновків була визначена необхідність проведення аналітичних епідеміологічних досліджень і підтримки діяльності популяційних реєстрів, перш за все національних канцер-реєстрів. Враховуючи факт, що опромінення після аварії для більшості населення було в діапазоні низьких доз, і лиш в окремих випадках серед учасників ЛНА, в діапазоні середніх або високих доз, експертами було зазначено, що достовірному визначенню може підлягати тільки надлишок захворюваності серед УЛНА, а також серед опромінених в перші тижні осіб наймолодших вікових груп.

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THYROID CANCER IN UKRAINIAN POPULATION GROUPS AFFECTED BY THE CHERNOBYL ACCIDENT

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ABSTRACT

The study goal was to investigate thyroid cancer morbidity in population groups affected by the Chernobyl catastrophe. The study period comprised 1994-2006 for clean-up workers and 1990-2006 for Chernobyl evacuees and residents of contaminated territories. A significant increase of thyroid cancer incidence was registered in all observed population groups. The most significant excess over the national level was identified in clean-up workers. This amounted to a factor of 5.9, while it was 5.5 for the evacuees and 1.7 for the residents. The highest thyroid cancer risk was observed in persons exposed to radioiodine in childhood and adolescence.

Key words: Chernobyl accident, Recovery operations worker, Evacuee, Resident of contaminated territory, Thyroid cancer

1 INTRODUCTION

Thyroid cancer is among the most frequent malignancies of endocrine glands. At the same time, its portion of total cancer incidence is comparatively small (less then 0.5 % in males and about 1 % in females). It is necessary to note the substantial variability of thyroid cancer incidence worldwide (Parkin, Whelan, Ferlay, Teppo, & Thomas, 2002). An excess of thyroid cancer was among the most expected consequences of the Chernobyl accident based on the high sensitivity of thyroid gland to the carcinogenesis associated with exposure to ionizing radiation as reported previously (Shore, 1992; Akiba, Lubin, & Ezaki, 1991). According to Illyin, Balonov, Buldakov, Bur'yak, Gordeev, Dement'ev, et al. (1990) the predicted possible amount of excess cases of malignant thyroid tumors for the whole population of those contaminated with ^{131}I raions (administrative units) was assessed to be 200 over a 30 year period. The percentage of malignant thyroid tumors in excess of the spontaneous level in the central regions of the Soviet Union, including Ukraine, might be 5 % among children and 0.9 % among adults. Mabuchi, Cardis, Preston, Ivanov, Okeanov, & Prisyazhniuk (1998) presented projections of substantial lifetime excess of thyroid cancer in inhabitants of the most contaminated regions that amounted to from 6 to 300 % depending on the average dose received. While realization of the dramatic scenario has been thoroughly studied and reported in those exposed as children (Cardis, Kesminiene, Ivanov, Malakhova, Shibata, Khrouch, et al., 2005; Kazakov, Demidchik, & Astakhova, 1992; Likhtarev, Kairo, Shpak, Tronko, & Bogdanova (1999); Tronko, Bobylyova, Bogdanova, Epstein, Likhtaryov, Markov, et al., 2003) only partial information on thyroid cancer in adults affected by the accident is available (Prysyazhnyuk, Gulak, Gristchenko, & Fedorenko, 2002; Ivanov, Tsyb, Ivanov, & Pokrovsky, 2004).

The stated goals of our study are to investigate thyroid cancer morbidity in Ukraine as a whole and in different population groups affected by the Chernobyl catastrophe and to evaluate quantitatively the realized incidence excess depending on the dose of ^{131}I exposure.

2 MATERIAL AND METHODS

The study period for Chernobyl accident recovery operations workers (CRW) was 1994-2006 and that for evacuees from the 30-km restriction zone around the Chernobyl NPP and residents of contaminated territories was 1990 –2006. The local cancer registry was used as the main data source for cancer cases among residents of the contaminated territories. It had been established to perform a retrospective (since 1980) and current collection of information on all cancer cases in the Luginy, Narodichy, and Ovruch districts of the Zhytomir region and the Borodyanka, Ivankiv, Polesskoye, and Chernobyl (1981-1985) districts of the Kyiv region. These six districts are referred to in the text below as the territories most heavily contaminated with radionuclides. Since 1989 when the National Cancer Registry of Ukraine was established, these two institutions have shared information on new cancer cases registered in contaminated territories.

From 1999 through 2004, this study was supported within the frame work of the French-German Initiative for Chernobyl, Project No 3 “Health effects of the Chernobyl accident”, Subprojects 3.1.1 “Solid cancer incidence in the most highly contaminated region of the Ukraine”, and 3.1.1S “Thyroid cancer in adolescents and adults in the most affected territories of the Ukraine after the Chernobyl accident”.

At the time of the accident, the total population of the most contaminated raions was 360.7 thousand including 74.4 thousand children aged 0-14 years (Prysyazhnyuk, Gristchenko, Zakordonets, Fuzik, Slipeniuk, & Ryzhak, 1995). In 2006, the population of six districts excluding the now evacuated Chernobyl district was 193.3 thousand including 29.9 thousand children (Derzhcomstat, State Committee of Statistics of Ukraine, 2005). For the data collection, all relevant medical documents (including emergency notifications of new cancer cases as well as death certificates) were obtained from all medical institutions where these patients were diagnosed and treated. These documents were cross-checked to eliminate duplicates and were then entered into the final data base. 12,458 new cases of cancer were registered in 1990-2006.

The data of the State Registry of Ukraine on Chernobyl victims were used to investigate cancer incidence among CRW (1986-1987 were the years of participation in clean-up activities) and among evacuees. The 1986-1987 data for CRW relate to a group of 105.4 thousand persons in 2006, namely those who resided in the Dnepropetrovsk, Donetsk, Kharkov, Kyiv, and Lugansk regions and in Kyiv City. In addition were the evacuees from Prypyat and the 30 km zone, who resettled in the territory of Ukraine, a group that included 53.4 thousand persons in 2006. The data were compared with the data base of the national cancer-registry. After this procedure, all duplicates and cases without validated diagnosis were eliminated. During 1994-2006, there were 6451 new cancer cases registered among CRW and, in 1990-2006, 2500 among evacuees (Prysyazhnyuk, Gristchenko, Fedorenko, Fuzik, Gulak, Slipeniuk, et al., 2002). The analysis was carried out with the standard methods of descriptive epidemiology: calculation of crude, age-specific, and age-adjusted incidence rates with standard errors and confidence intervals. The world population structure was used as the standard. For indirect standardization (calculation of standardized incidence ratio – SIR) the age-specific cancer incidence rates of the Ukrainian population in 1998 were used. To reveal possible tendencies, linear regression coefficients were calculated.

3 RESULTS AND DISCUSSION

In the 20 years following the Chernobyl accident in Ukraine, as a whole, thyroid cancer incidence exceeded spontaneous rates a factor of two in males and three in females. (Figure 1)

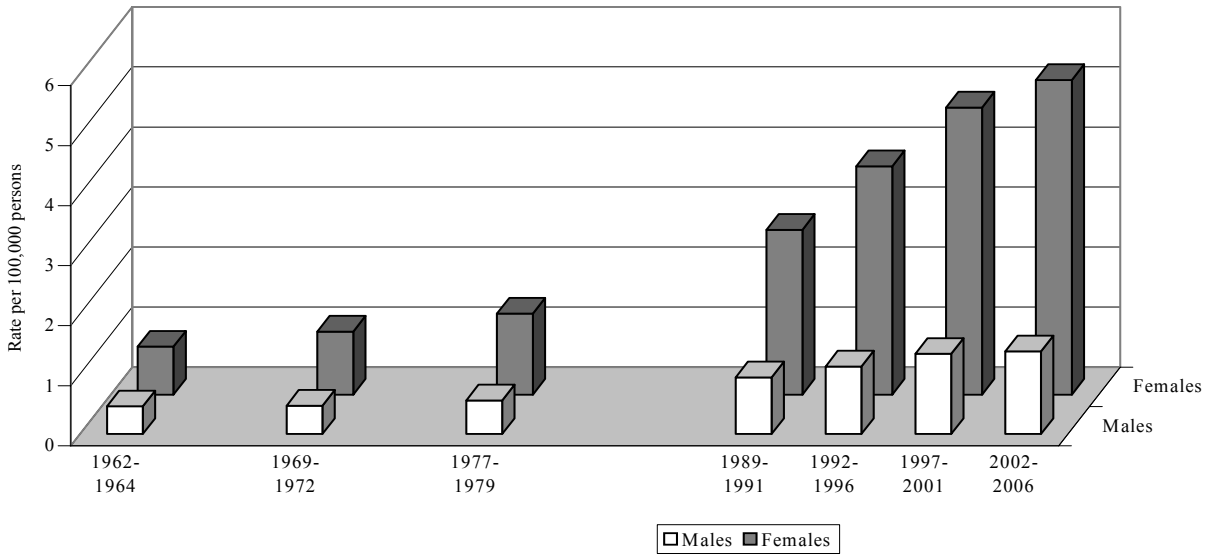

Figure 1. Age-standardized average annual thyroid cancer incidence rates in Ukraine in separate time periods (males and females)

The first cases of thyroid cancer in children who resided in the most contaminated territories were observed in 1990 (Prysyazhnyuk, Pjatak, Buzunov, & Beral, 1991). Before that time, no case of the disease had been registered for the children of these territories.

Starting from that period, an increasing incidence was marked not only in children (Tronko & Bogdanova, 1997) but also in adolescents and adults (Prysyazhnyuk, Romanenko, Grystchenko, Zakordonets, Fedorenko, Fuzik et al., 2004). Investigation conducted in the frame of the French-German Initiative for the period 1990-1999 in 3 oblasts with substantial ^{131}I fall-outs showed for the first time a relationship between the level of radioiodine fall-outs and the thyroid cancer incidence rate (Table 1).

Table 1. Truncated age-adjusted incidence rate (TASR) in 1991-1999 in adolescents and adults inhabiting the Zhytomir, Kyiv, and Cherhigiv regions in territories with different levels of ^{131}I deposition

Gender	TASR per 100 000 population on territories of ^{131}I deposition (kBq/m^2)		
	≤ 100	100-200	≥ 200
Male	1.53 ± 0.26	2.20 ± 0.20	2.56 ± 0.25
Female	3.94 ± 0.26	10.36 ± 0.41	10.21 ± 0.46

The truncated age-standardized incidence rate in territories with a level of contamination <100 kBq m^{-2} did not exceed 2 cases per year per 100,000 males and 5 cases per year per 100,000 females. However, in territories with medium and high levels of contamination (100-200 kBq m^{-2} and >200 kBq m^{-2}**,** respectively), a significant increase in the thyroid cancer incidence rate was registered. The excess amounted to 4 cases per year per 100,000 males and 16 cases per year per 100,000 females in 1998-1999. The effect of the exposure to radioiodine, i.e. the excess of thyroid cancer, kept increasing during the study period.

A comparative analysis of the thyroid cancer incidence rate in different groups of the affected population (Table 2) suggests that the most significant excess over the national level during the study period occurred in CRW. This amounted to a factor of 5.9, while it was 5.5 for the evacuees. Among the residents of the territories that were most heavily contaminated with radionuclides, a statistically significant excess of thyroid cancer incidence (by a factor of 1.7) was registered for the time period 1990-2006.

Table 2. Standardized incidence rates (SIR) values for thyroid cancer (Code ICD-10 C73) in different groups of the Ukrainian population affected by the Chernobyl accident

Groups of observation (period of observation)	Observed numbers of cases	Expected numbers of cases	SIR (%)	95% CI
Residents of contaminated territories (1990-2006)	283	169.4	167.0	147.6 - 186.5
Recovery operation workers 1986-1987 (1994-2006)	274	46.1	594.2	523.8 -664.6
Evacuees from 30km zone (1990-2006)	213	39.1	544.9	471.7 - 618.1

These figures illustrate the lack of effectiveness of the prophylactic measures taken by medical authorities in 1986 (stable iodine administration) in order to prevent radioiodine accumulation in thyroid.

The highest thyroid cancer risks were observed in persons exposed to radioiodine in childhood and adolescence. Comparative medico-geographical analysis in regions of Ukraine tested the average accumulated thyroid doses (mGy) in young persons (1-18 years old) at the moment of accident and thyroid cancer incidence rate in this cohort 20 years later.

There is a correspondence between factorial (doses) and observed results (thyroid cancer incidence rate in 2006 in irradiated cohort 1-18 years old at the moment of accident) (r=0.5023, P, 0.01). This is the reason we searched for the linear regression equation between dose and incident rate (Figure 2).

The abscissa axis represents the average accumulated dose (Gy), and the ordinate axis represents the incidence rate per 10,000 population. Therefore, the regression coefficient **b** actually reflects a rate change per 10,000 of 1 Gy. That is, the excess absolute risk is $4{,}92*10^{-4}$ prsGy. The ratio of **b** to **a** (the incidence rate for an average accumulated dose equal to 0) indicates an excess relative risk of 22,2/Gy.

Note that in this cohort attributive risk = $\frac{ERR}{(1+ERR)} \cdot 100$ = 95.7%. (1)

Therefore, most thyroid cancer cases in this cohort have a radiogenic origin.

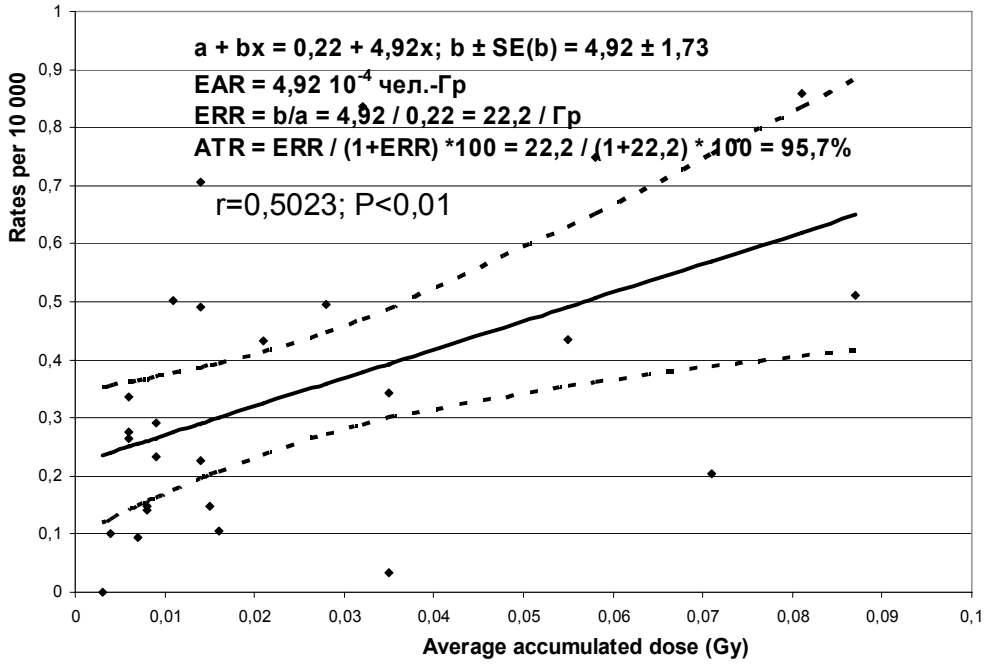

Figure 2. Parameters of a linear regression equation between average regional thyroid doses of children and adolescents (1-18 years old) in 1986 and thyroid cancer incidence rates in this cohort in 2006 in regions of Ukraine

During the long term observation of cancer incidence rates, new diagnostic methods and procedures, which could influence morbidity figures, were implemented. This is called the screening-technological effect. A method of eliminating this phenomenon was proposed and used in this study. The comparative analysis of two cohorts [1982-1986 years of birth (exposed to radioiodine) and 1987-1991 years (non-exposed)] in regions with the highest integral deposition of radioiodine (Kyiv, Chernigiv, and Zhytomir regions) was carried out (Figure 3).

Because both cohorts were screened in the same manner, conclusions about the effect of irradiation in successive attained age periods could be made. In the age period 10-14 years, the risk for cohort 1982-1986 of thyroid cancer is 9.7 times higher than for the 1987-1991 cohort; for 15-19 years the risk is 3.4 times higher.

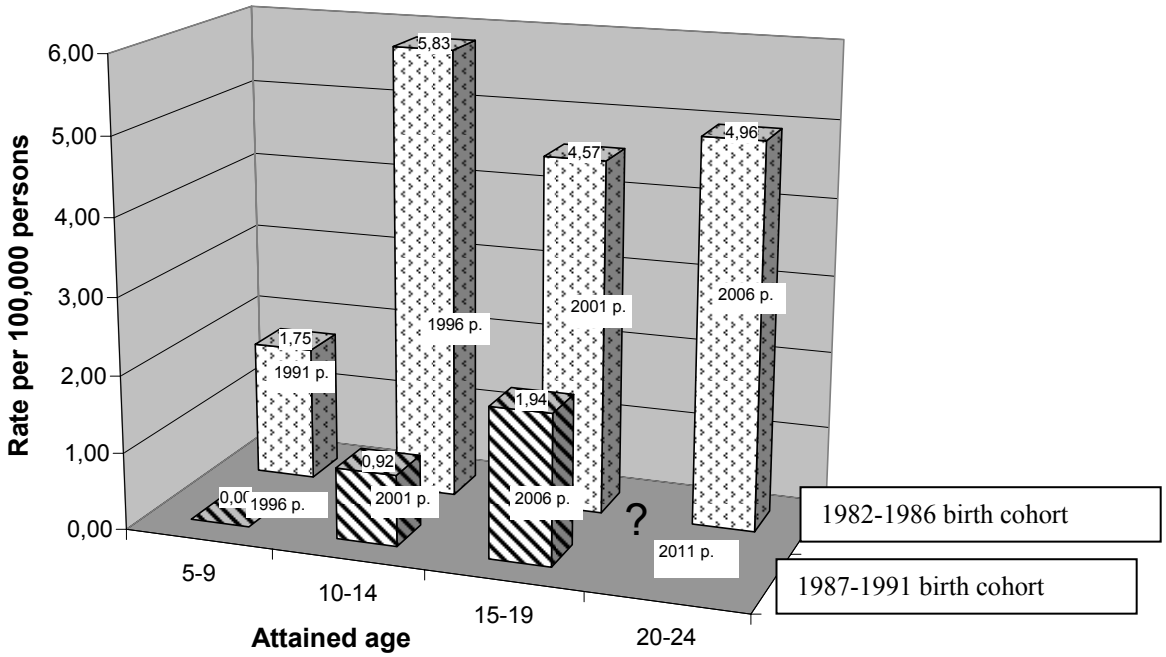

Figure 3. Dynamics of the thyroid cancer incidence in birth cohorts 1982-1986 and 1987-1997 (Zhitomirska, Kyivska, and Chernihivska oblasts)

It is necessary to note that in territories with low doses of thyroid irradiation, the incidence does not differ substantially in the identified birth cohorts.

4 CONCLUSION

In all population groups affected by the Chernobyl accident, a significant increase of thyroid cancer incidence was registered. The increase was found not only in children but also in adolescents and adults. It appears to be associated, at least partly, with the fall-out of radioiodine. At the same time, we cannot disclaim the significant role that external irradiation played in the total dose received by clean-up workers.

It was difficult to evaluate completely in the present descriptive study the contribution of increased screening of the thyroid glands to the observed increase of thyroid cancer. Based on the experience of previous studies on health effects of irradiation, the excess of solid cancer including that of the thyroid was observed decades after exposure. Therefore, we should continue to monitor thyroid cancer in groups of affected populations. The data suggest the necessity for epidemiological monitoring of thyroid cancer and a concentration of efforts to perform analytical epidemiological studies that will evaluate radiation risks at low doses of irradiation.

The documentation of dosimetric information will be essential for future attempts to examine – and possibly improve – current estimates of the risk of radiation associated thyroid cancer.

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ORIGINAL PAPER

Thyroid cancer incidence in Ukraine: trends with reference to the Chernobyl accident

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Abstract For the first time, a comparative analysis of thyroid cancer incidence in Ukraine after the Chernobyl accident was done in a cohort that is almost as large as the general population. On the basis of thyroid doses from radioactive iodine in individuals aged 1–18 years at the time of accident, geographic regions of Ukraine with low and high average accumulated thyroid doses were established and designated "low-exposure" and "high-exposure" territories, respectively. A significant difference of thyroid cancer incidence rates as a function of time between the two territories was found. That is, the increase in the incidence was higher in high-exposure regions than in low-exposure regions. The incidence rates varied substantially among the different attained age-groups, especially in the youngest one (up to 19 years old). The analysis that was adjusted for screening and technological effects also indicated that in the high-exposure regions, thyroid cancer incidence rates at the age of diagnosis of 5–9, 10–14 and 15–19 years were significantly higher in those born in 1982–1986 compared to those born in 1987–1991, while in the low-exposure regions, no significant difference was observed. The observed probable excess of radiation-induced thyroid cancer cases in adults exposed to radioactive iodine from the Chernobyl accident, especially in females, may be due to the high power of the present study. However, it should be noted that our investigation was not essentially free from ecological biases.

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Introduction

Thyroid cancer is the most common malignancy of the endocrine system. However, it accounts only for a small fraction of all human cancers (Franceschi et al. 1993). In 1980s, the annual incidence of thyroid cancer varied considerably in different European registries, ranging from 0.6 to 6.2 in males and from 1.0 to 8.3 in females per 1,00,000 individuals (Parkin et al. 1992).

Before the accident at the Chernobyl nuclear power plant in 1986, the thyroid cancer incidence rate in Ukraine increased slowly but steadily. After the accident, this increase became steeper (Prysyazhnyuk et al. 2002): From 1989 to 2007, the thyroid cancer incidence rate increased from 0.9 to 1.6 in males and from 2.7 to 6.2 in females, per 1,00,000 individuals. The overall fraction of thyroid cancer among all human cancers increased about twofold for both genders: from 0.33 to 0.62% in males and from 1.59 to 3.28% in females (Gulak et al. 2004; Shshepotin et al. 2009).

The vulnerability of the thyroid to ionizing radiation has already been known before the accident (BEIR-V 1990); therefore, it gained particular attention after the Chernobyl accident. For this reason, since 1989, thyroid cancer has been singled out as a separate entry in the official statistics on cancer incidence by the Ministry of Health of Ukraine, while before it was included into the category "others".

Furthermore, thyroid cancers diagnosed up to an age of 29 years were specified by 5-year age classes (Winkelmann et al. 1998), allowing to obtain more detailed information about cancer incidence in children and adolescents.

Due to radioiodine released to the environment after the Chernobyl accident, a large number of inhabitants of Ukraine, Russia and Belarus received radiation doses to the thyroid that were much higher than doses to other organs and tissues (UNSCEAR 2000). It is also remarkable that the Chernobyl accident became an issue not only in adjacent but also in remote countries and promoted research of its possible consequences in respective populations (e.g., Tirmarche and Catelinois 2002; Verger et al. 2003).

The increase in thyroid cancer is one of the most recognized health consequences of the Chernobyl accident in those territories of Ukraine, Belarus and Russia surrounding the Chernobyl nuclear power plant. In fact, the first radiation-induced thyroid cancer cases were registered 4 years after the Chernobyl accident (Prysyazhnyuk et al. 1991, 1995; Kazakov et al. 1992).

A number of studies estimated thyroid cancer risk of people exposed to Chernobyl radiation in childhood and adolescence (Sobolev et al. 1996; Demidchik et al. 2002; Ivanov et al. 2002, 2004; Kenigsberg et al. 2002; Likhtarov et al. 2006; Davis et al. 2004; Jacob et al. 2006; Kopecky et al. 2006). Although significantly increased radiation risk has been demonstrated in all of them, estimates vary quite widely.

As to adult population, three different affected groups have been commonly explored: recovery operation workers, evacuees and residents of the most heavily contaminated territories. In all these groups, an excess of thyroid cancer incidence was registered (compared with national levels), but it is disputable to which extent this is due to ionizing radiation, because of the potential influence of screening and introduction of modern ultrasound diagnostic equipment (Prysyazhnyuk et al. 2007; Ivanov et al. 2003, 2008).

Most of the previous studies on thyroid cancer incidence were fragmentary and covered only particular groups of the population affected by the Chernobyl accident. The objective of the present study was to elucidate the trends of thyroid cancer incidence in the whole Ukrainian population.

Materials and methods

Information on thyroid cancer cases in Ukraine from 1989 through 2008 was collected from the Ukrainian cancer registry; from 1989 through 2007, gender- and 5-year age-specific annual data for the population of each region in the country were obtained from official publications of the State Committee of Statistics.

All regions of Ukraine were classified into two groups based on ^{131}I thyroid doses that were reconstructed for the entire Ukrainian population aged 1–18 years at the time of the accident (Likhtarov et al. 2005). Assuming that the ranking of regions by the distribution of accumulated dose in those individuals aged 1–18 years was similar to that in older age-groups in the same regions, we designated the regions "high-exposure" if thyroid dose exceeded 35 mGy (Fig. 1).

Although the average individual thyroid dose was 32 mGy in Kyiv city, we included it in the high-exposure regions, because a significant proportion of all recovery operation workers (over 23%) and evacuees from the city of Prypyat and from the 30-km zone (over 15%) reside in Kyiv city. These high numbers are characteristic for the

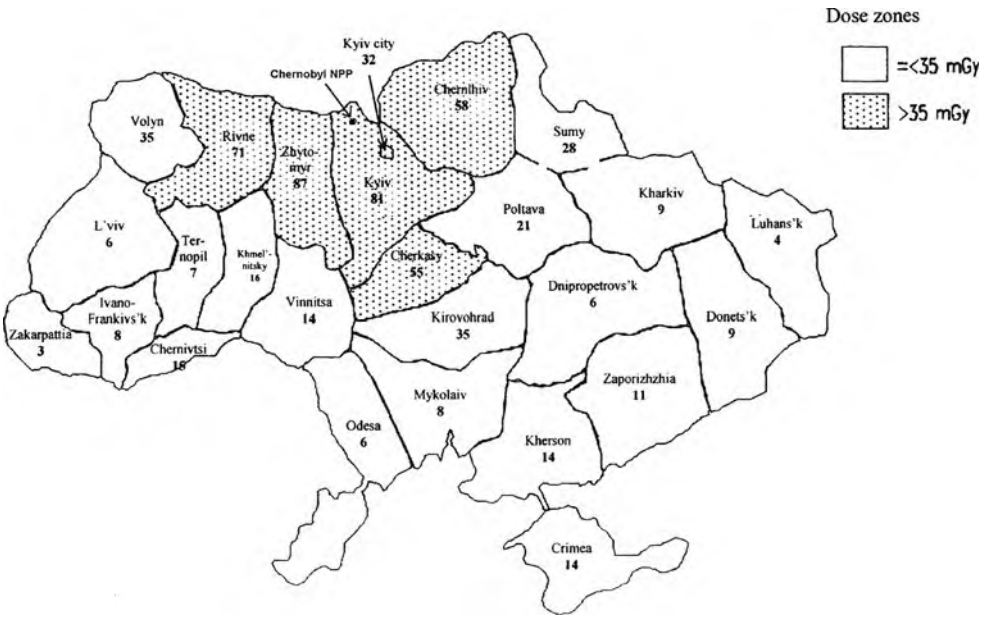

Fig. 1 Average accumulated thyroid doses (*bold numbers*, given in mGy) in all regions of Ukraine, for individuals aged 1–18 years at the time of the Chernobyl accident (Likhtarov et al. 2005)

Kiev region only, while the fraction of recovery operation workers and evacuees in all other high-exposure regions is substantially lower. For instance, these two risk groups account for 4.6 and 2.6%, respectively, in Chernihiv region (Bobylyova 1999). It should also be noted that according to our calculations that were done on the basis of the available data (UNSCEAR 2000), the average thyroid dose of the evacuees is 328 mGy.

Thus, Cherkasy, Chernihiv, Kyiv, Rivne, Zhytomyr regions and Kyiv city were designated as high-exposure regions, while all other locations were designated as low-exposure regions.

We calculated both the age-specific and age-adjusted thyroid cancer incidence rates for each year and for aggregated time periods, where age adjustment was done using the World Standard Population. For aggregated age-groups (such as 0–19, 20–39, 40–59, 60+ years), truncated age-standardized incidence rates (TASR) were calculated. The reference period was limited to 1989 only because the first radiation-induced thyroid cancer cases were registered in 1990 (Prysyazhnyuk et al. 1991, 1995; Kazakov et al. 1992) and because we considered 1989 the last year of the latency period. The data for earlier years were not available, as already pointed out above.

The rate ratio (RR) was used to compare thyroid cancer incidence rates between high-exposure and low-exposure regions and calculate 95% confidence intervals (95% CI) assuming Poisson distribution for the annual incidence of thyroid cancer (Rothman 1986). The lower and upper limits of the confidence interval for the ratios of two age-standardized rates (ASR_1 and ASR_2) are: $(ASR_1/ASR_2)^{1\pm(z_{\alpha/2}/X)}$, where $z_{\alpha/2}$ denotes the $100(1-\alpha/2)$ percentile of the standard normal distribution, and $z_{\alpha/2}=1.96$ for $\alpha=0.05$. For X, we used an approximation proposed by Smith (1987): $X=\frac{(ASR_1-ASR_2)}{\sqrt{\{SE(ASR_1)\}^2+\{SE(ASR_2)\}^2}}$, where SE denotes the standard error.

Results

The thyroid cancer incidence rate and its dynamics in the two groups of regions were quite different. The level and average annual increase of thyroid cancer incidence were higher in the high-exposure regions than in the low-exposure regions, both for males and females (Fig. 2).

Throughout the period of the present study (1989–2008), age-adjusted thyroid cancer incidence rate in females of the high-exposure regions increased from 3.34 to 10.99 per 1,00,000, i.e., 3.3-fold, while in females of the low-exposure regions, it increased from 2.51 to 5.69 per 1,00,000, i.e., 2.3-fold. In contrast, in males, the thyroid cancer incidence rate was 0.87 per 1,00,000 at the beginning of the

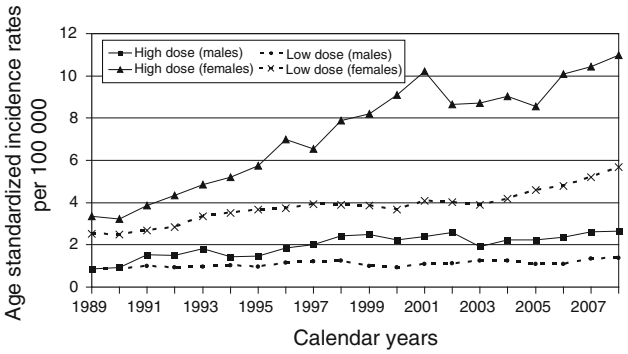

Fig. 2 Trends in thyroid cancer incidence from 1989 through 2008 in Ukraine by gender and dose category

observation (1989) for both the high-exposure and low-exposure regions. In 2008, it increased to 2.64 in the high-exposure and 1.37 in the low-exposure regions, corresponding to factors 3.0 and 1.6, respectively. The slopes of the regression lines through the four trends in Fig. 2 are as follows: 0.079 (standard error (SE) = 0.011) for males of the high-exposure regions and 0.019 (SE = 0.004) for those of the low-exposure regions; 0.405 (SE = 0.029) for females of the high-exposure regions and 0.133 (SE = 0.011) for those of the low-exposure regions. This means that in the high-exposure regions, the thyroid cancer incidence rate increased faster compared to that in the low-exposure regions both for males and females, over the period of observation. The difference in the regression coefficients deduced for the high- and low-exposure regions is statistically significant for both genders ($p < 0.01$).

Table 1 compares rate ratios of truncated age-standardized incidence rates (TASR) for thyroid cancer by age-group and sex across the five-year intervals, for the high-exposure regions. Marked increases in RRs were noted for both males and females. The increases were most pronounced for those individuals aged 0–19 years at the time of diagnosis, being 13.99 and 5.55 in males and females, respectively, when the rates for the 1995–1999 period were compared with those of 1989. The RRs decreased steadily during the periods of 2000–2004 and 2005–2008 compared to the RR of 1995–1999, and the increase was already non-significant both for males and females diagnosed in 2005–2008. In all age-groups except for 0–19 years at the time of diagnosis, the RR steadily increased both in males and females; this increase was statistically significant for nearly all periods. The exceptions were the period of 1990–1994 for males and females diagnosed at 40–59 years and 60+ years, and 1995–1999 for males diagnosed at 60+ years.

In the low-exposure regions, an increase in thyroid cancer incidence in males was noted only among those diagnosed at 20–39 years in 2000–2004 and 2005–2008,

Table 1 Rate ratios by gender and age at diagnosis for thyroid cancer incidence rates per 1,00,000 among the residents of the high-exposure regions in Ukraine, 1989–2008

Year of diagnosis	Males				Females			
	n	TASR	RR	95% CI	*n*	TASR	RR	95% CI
0–19 years at diagnosis								
1989	1	0.06	1		5	0.34	1	
1990–1994	56	0.71	11.58	5.02–26.71	99	1.29	3.78	2.18–6.55
1995–1999	71	0.86	13.99	6.47–30.26	150	1.89	5.55	3.47–8.87
2000–2004	60	0.71	11.48	5.08–25.97	110	1.36	4.00	2.35–6.81
2005–2008	6	0.10	1.54	0.24–9.81	41	0.09	1.77	0.82–3.79
20–39 years at diagnosis								
1989	8	0.52	1		56	3.46	1	
1990–1994	82	1.10	2.11	1.21–3.68	316	4.00	1.16	1.13–1.18
1995–1999	106	1.47	2.81	1.71–4.63	475	6.34	1.83	1.71–1.97
2000–2004	143	2.05	3.94	2.53–5.13	706	9.99	2.89	2.64–3.17
2005–2008	137	2.42	4.65	3.00–7.21	614	8.47	2.45	2.25–2.67
40–59 years at diagnosis								
1989	20	1.69	1		103	7.85	1	
1990–1994	131	2.24	1.33	0.86–2.03	609	9.34	1.19	0.98–1.45
1995–1999	224	3.83	2.27	1.61–3.20	1,061	15.75	2.01	1.71–2.35
2000–2004	235	4.07	2.41	1.73–3.37	1,396	20.68	2.63	2.29–3.03
2005–2008	256	5.27	3.12	2.29–4.27	1,338	18.58	2.27	2.05–2.74
60+ years at diagnosis								
1989	18	3.14	1		66	5.33	1	
1990–1994	108	3.35	1.07	0.66–1.74	397	6.31	1.18	0.93–1.51
1995–1999	148	4.53	1.44	0.94–2.21	606	11.10	2.08	1.71–2.54
2000–2004	178	5.06	1.61	1.07–2.42	747	13.22	2.48	2.06–2.98
2005–2008	149	5.78	1.84	1.24–2.74	661	13.42	2.52	2.09–3.04

n number of cases, *CI* confidence interval

and among those diagnosed at 40–59 years in any time period. In females, the RR was significantly greater than unity for all periods and all diagnostic ages, except those diagnosed at 0–19 and 60+ years in 1990–1994 (Table 2).

Table 3 compares ratios between TASRs for thyroid cancer in the high-exposure and low-exposure regions by age-group and sex across time periods: 1989, 1990–1994, 1995–1999, 2000–2004 and 2005–2008. While the ratios of incidence rates for 1989 were generally comparable for the high- and low-exposure regions, the RRs in the three age-groups (except 0–19 years) increased for all of the later time periods. In those diagnosed at 0–19 years, it, however, passed its peak in 1990–1994 and sharply decreased in 2005–2008.

Figure 3 presents thyroid cancer incidence at the age of diagnosis of 5–9, 10–14, 15–19 and 20–24 years for those individuals of the high- and low-exposure regions born in 1982–1986 and 1987–1991. In the high-exposure regions, thyroid cancer incidence rates at the age of diagnosis of 5–9, 10–14 and 15–19 years were significantly higher in those born in 1982–1986 compared to those born in 1987–1991, while in the low-exposure regions, no such difference was observed.

Since the level of soil ^{131}I contamination is known to have been essentially zero in 1987 (Shibata et al. 2001), it is possible to use the maximal values (to avoid an overestimation of the screening effect) of the thyroid cancer incidence rate in the remaining three groups of individuals presented in this figure (conditionally, low-exposed)—residents of the high-exposure regions born in 1987–1991 and of the low-exposure regions at each age of diagnosis—for estimating the rate in individuals not affected by radioactive iodine. At ages of 5–9, 10–14, 15–19 and 20–24 years, these were 0.10 (low-exposure, born in 1987–1991), 0.49 (low-exposure, born in 1982–1986), 1.40 (high-exposure, born in 1987–1991) and 1.50 (low-exposure, born in 1982–1986) per 1,00,000, respectively. Subtraction of these values from the corresponding rates in the high-exposure regions for individuals born in 1982–1986 yields the estimates of radiation-induced thyroid cancer incidence per 1,00,000: 0.84 (0.94–0.10) for those diagnosed at

Table 2 Rate ratios by gender and age at diagnosis for thyroid cancer incidence rates per 1,00,000 among the residents of the low-exposure regions in Ukraine, 1989–2008

Year of diagnosis	Males				Females			
	n	TASR	RR	95% CI	*n*	TASR	RR	95% CI
0–19 years at diagnosis								
1989	8	0.13	1		12	0.19	1	
1990–1994	39	0.12	0.94	0.43–2.04	76	0.24	1.25	0.71–2.20
1995–1999	62	0.19	1.49	0.79–2.83	142	0.44	2.26	1.46–3.51
2000–2004	49	0.15	1.16	0.57–2.36	110	0.35	1.82	1.13–2.95
2005–2008	27	0.12	0.94	0.42–2.09	88	0.41	2.12	1.31–3.44
20–39 years at diagnosis								
1989	32	0.52	1		145	2.22	1	
1990–1994	177	0.55	1.07	0.74–1.55	920	2.88	1.30	1.26–1.34
1995–1999	203	0.65	1.27	0.90–1.79	1,136	3.64	1.64	1.57–1.72
2000–2004	208	0.74	1.43	1.03–1.99	1,041	3.66	1.65	1.58–1.73
2005–2008	217	0.97	1.88	1.38–2.56	1,051	4.69	2.12	2.00–2.25
40–59 years at diagnosis								
1989	69	1.40	1		290	5.28	1	
1990–1994	482	1.93	1.37	1.10–1.72	1,733	6.32	1.20	1.06–1.35
1995–1999	497	2.11	1.50	1.20–1.87	2,292	8.44	1.60	1.44–1.77
2000–2004	520	2.28	1.63	1.32–2.01	2,550	9.45	1.79	1.62–1.97
2005–2008	457	2.32	1.65	1.33–2.05	2,781	11.98	2.27	2.07–2.49
60+ years at diagnosis								
1989	83	3.46	1		304	6.41	1	
1990–1994	402	3.10	0.90	0.70–1.14	1,667	6.68	1.04	0.92–1.18
1995–1999	509	3.72	1.07	0.86–1.35	1,864	7.72	1.20	1.07–1.35
2000–2004	494	3.44	0.99	0.79–1.25	1,823	7.46	1.16	1.04–1.31
2005–2008	401	3.74	1.08	0.86–1.36	1,701	9.68	1.51	1.36–1.68

n number of cases, *CI* confidence interval

Table 3 Rate ratios (RR) by gender and age at diagnosis for thyroid cancer incidence rates per 1,00,000 between residents of the high-exposure and low-exposure regions in Ukraine, 1989–2008

Age at diagnosis	Year of diagnosis									
	1989		1990–1994		1995–1999		2000–2004		2005–2008	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
0–19										
Males	0.48	0.09–2.52	5.95	3.56–10.55	4.53	2.85–7.21	4.78	2.86–7.98	0.80	0.35–1.83
Females	1.77	0.52–6.02	5.34	3.53–8.10	4.33	3.17–5.93	3.88	2.73–5.52	1.47	0.98–2.21
20–39										
Males	1.01	0.47–2.20	1.99	1.45–2.73	2.24	1.67–3.00	2.79	2.13–3.67	2.50	1.91–3.27
Females	1.56	1.10–2.21	1.39	1.21–1.60	1.74	1.54–1.97	2.73	2.42–3.08	1.80	1.61–2.02
40–59										
Males	1.20	0.71–2.03	1.16	0.95–1.42	1.82	1.51–2.19	1.78	1.49–2.13	2.27	1.88–2.74
Females	1.49	1.15–1.91	1.48	1.33–1.64	1.87	1.71–2.03	2.19	2.02–2.37	1.55	1.44–1.67
60+										
Males	0.90	0.55–1.49	1.08	0.87–1.34	1.22	1.00–1.48	1.47	1.22–1.78	1.54	1.25–1.91
Females	0.83	0.65–1.07	0.94	0.85–1.05	1.44	1.30–1.59	1.77	1.60–1.96	1.39	1.26–1.53

CI confidence interval

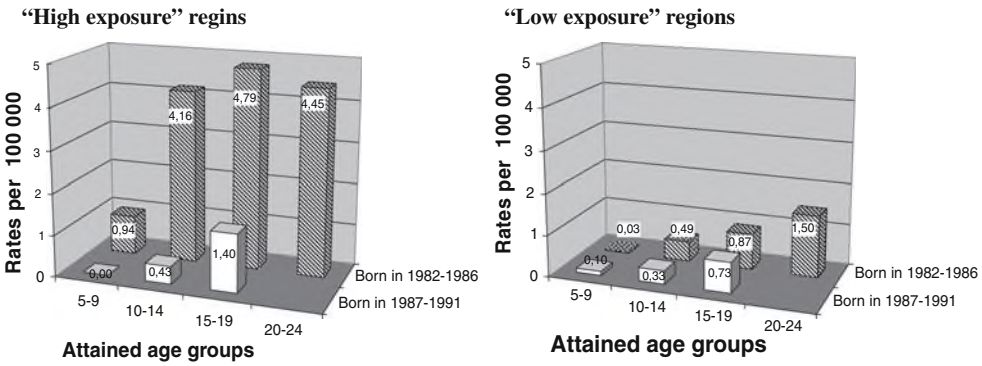

Fig. 3 Thyroid cancer incidence rate per 1,00,000 by birth year and age at diagnosis in the high-exposure regions (*left panel*) and low-exposure regions (*right panel*)

5–9 years, 3.67 (4.16–3.49) for those at 10–14 years, 3.39 (4.79–1.40) for those at 15–19 years and 2.95 (4.45–1.50) for those at 20–24 years. Thus, the proportion of radiation-induced thyroid cancer cases can be estimated as 89.2% in those diagnosed at 5–9 years; 88.3% at 10–14 years; 70.8% at 15–19 years and 66.4% at 20–24 years.

Table 4 summarizes trends for 4 years of 1991, 1996, 2001 and 2006 in terms of RR for age-specific thyroid cancer incidence rates in females of the high- and low-exposure regions by age at the time of the Chernobyl accident. Although some irregularities exist, the data indicate that except for those exposed at 0–4, 5–9, 15–19 and 50–54 years, the RR reached a maximum in 2001. In females exposed at 0–4 years, the RR steadily decreased since 1991. The trends in males, however, were not as clear as in females except for those exposed at 0–4 years (Table 5).

Discussion

The present analysis revealed significant differences in trends of the thyroid cancer incidence rate in the two groups of regions investigated: the increase in this malignancy was higher in high- than in low-exposure regions; the incidence rate varied among the attained age-groups. The steepest increase was registered in the young age-groups (up to 19 years) of the high-exposure regions, suggesting that the thyroid is particularly vulnerable to radiation in childhood and adolescence. The incidence rate in these groups substantially decreased in 2005–2008 probably because the majority of the members of these groups (and all since 2006) are individuals born in 1987 or later who were not exposed to ^{131}I from the Chernobyl accident.

In the groups of other ages at diagnosis, the age-specific incidence rate was characterized by a steady increase that was significantly higher in the high- than in the low-exposure regions. The least clear tendency was observed in the oldest age-group of 60+ years in the low-exposure regions. This could be explained by the lower vulnerability of the thyroid to radiation in adults and by a possible increase in the period of latency with age.

The significant increase in thyroid cancer incidence observed in the low-exposure regions for all age-groups at

Table 4 Rate ratios (95% confidence intervals) for age-specific thyroid cancer incidence rates in females of the high- and low-exposure regions in Ukraine by age at the time of the Chernobyl accident and year of diagnosis

Age at the time of the Chernobyl accident (years)	Year of diagnosis							
	1991		1996		2001		2006	
0–4	12.33	(0.54, 280.40)	10.83	(3.48, 33.71)	5.60	(2.29, 13.74)	2.62	(1.40, 4.92)
5–9	28.63	(2.16, 380.15)	2.41	(1.02, 5.70)	3.42	(1.75, 6.67)	2.28	(1.36, 3.85)
10–14	2.82	(0.82, 9.77)	2.12	(0.87, 5.16)	3.64	(2.15, 6.17)	2.46	(1.54, 3.95)
15–19	1.30	(0.44, 3.84)	1.38	(0.73, 2.63)	2.29	(1.35, 3.88)	2.37	(1.53, 3.68)
20–24	1.00	(0.44, 2.29)	1.74	(1.04, 2.92)	2.64	(1.72, 4.06)	2.13	(1.47, 3.09)
25–29	1.98	(1.09, 3.60)	1.67	(1.08, 2.60)	2.68	(1.82, 3.95)	2.46	(1.79, 3.38)
30–34	1.97	(1.17, 3.33)	2.06	(1.37, 3.11)	2.41	(1.74, 3.34)	2.27	(1.69, 3.06)
35–39	0.95	(0.58, 1.56)	1.82	(1.25, 2.65)	2.02	(1.48, 2.76)	1.73	(1.30, 2.30)
40–44	1.70	(0.97, 2.98)	1.71	(1.14, 2.57)	2.44	(1.59, 3.77)	1.63	(1.10, 2.42)
45–49	1.66	(1.09, 2.54)	1.80	(1.26, 2.59)	2.31	(1.65, 3.24)	1.95	(1.38, 2.78)
50–54	1.32	(0.77, 2.27)	2.59	(1.61, 4.15)	2.04	(1.26, 3.30)	1.28	(0.75, 2.19)
55–59	0.83	(0.53, 1.31)	0.93	(0.61, 1.41)	1.57	(1.01, 2.44)	0.99	(0.62, 1.57)

Table 5 Rate ratios (95% confidence intervals) for age-specific thyroid cancer incidence rates in males of the high- and low-exposure regions in Ukraine by age at the time of the Chernobyl accident and year of diagnosis

Age at the time of the Chernobyl accident (years)	Year of diagnosis							
	1991		1996		2001		2006	
0–4	NA	NA	5.91	(1.53, 22.86)	5.40	(1.78, 16.38)	4.91	(1.29, 18.77)
5–9	16.40	(0.87, 310.53)	2.93	(0.66, 12.98)	2.39	(0.60, 9.54)	4.38	(1.29, 14.85)
10–14	0.68	(0.10, 4.40)	3.08	(0.43, 21.80)	3.86	(1.05, 14.24)	1.80	(0.63, 5.12)
15–19	4.05	(0.46, 35.34)	0.37	(0.08, 1.61)	1.69	(0.44, 6.56)	1.31	(0.48, 3.54)
20–24	6.32	(1.06, 37.70)	0.79	(0.25, 2.48)	2.97	(1.13, 7.80)	4.09	(1.55, 10.79)
25–29	2.52	(0.70, 9.11)	2.37	(0.85, 6.60)	2.71	(1.17, 6.24)	1.24	(0.56, 2.74)
30–34	0.51	(0.16, 1.66)	2.89	(1.29, 6.45)	1.66	(0.71, 3.89)	2.48	(1.04, 5.90)
35–39	0.42	(0.14, 1.26)	2.20	(1.04, 4.65)	2.64	(1.26, 5.52)	2.43	(1.17, 5.06)
40–44	1.13	(0.36, 3.58)	1.08	(0.43, 2.73)	2.08	(0.82, 5.26)	1.88	(0.83, 4.25)
45–49	0.64	(0.30, 1.36)	1.80	(0.88, 3.67)	0.99	(0.51, 1.93)	1.75	(0.84, 3.65)
50–54	1.50	(0.70, 3.25)	0.45	(0.18, 1.11)	2.00	(0.81, 4.97)	2.36	(0.80, 6.94)
55–59	2.18	(0.85, 5.59)	0.84	(0.37, 1.91)	1.07	(0.35, 3.28)	1.79	(0.68, 4.76)

NA not available

diagnosis was not as steep as in the high-exposure regions. This increase could be due to both an increase in background and screening effects.

The results of the present study evidently confirm the high vulnerably of young age-groups to radiation carcinogenesis. Especially sensitive is the youngest age-group born in 1982–1986 aged 0–4 years at the time of the Chernobyl accident. The observed dramatic increase in the thyroid cancer incidence rate in this age-group is predominantly attributed to ionizing radiation. This conclusion is strongly suggested by the results obtained when the incidence in this age-group was compared between the high- and low-exposure regions, where other confounding and modifying non-radiation factors (e.g., quality of registration, screening) were similar.

As for the incidence in adults, rate ratios in females significantly exceeded unity in 1996, 2001 and 2006 in those exposed at ages of 20–49 years, reaching the maximum in 2001 (Table 4), while in males, this tendency was less clear (Table 5). One may conceive from these results that there is a probable excess in radiation-induced thyroid cancer cases in exposed people, especially in females, irrespectively of age at the accident. This conclusion seems quite important because even relatively recent papers report a lack of convincing evidence of radiation excess in thyroid cancer in exposed adults (Ivanov et al. 1999; Moysich et al. 2002; Hatch et al. 2005; Williams 2008; Ron 2007).

The present study also suggests that the latency period of radiation-induced thyroid cancer development may depend on age at exposure: the peak of rate ratio in the youngest age-groups at the time of the Chernobyl accident was in 1991, but in elder ages it is shifted to later years (Tables 4, 5). Previous investigations into this problem are very limited, but Dedov et al. (1993) pointed out the possibility of such a dependence in patients subjected to radiation therapy. Further studies are necessary to confirm these observations.

It should be noted that the character of the data presented and the analytical methods used are very similar to those by Mahoney et al. (2004) who explored the trends of thyroid cancer incidence and impact of the Chernobyl accident in Belarus. These authors concluded that radiation exposure led to an increase in thyroid cancer incidence rate not only in children and adolescents but in adults as well. In particular, an excess of thyroid cancer was found in the age-group of 35–54 years at diagnosis. Since their study was completed in 2001, this age-group included persons who already were adults in 1986. However, calculations were performed only with regard to age at diagnosis, while age at exposure is also important for the evaluation of risk factors in radiation carcinogenesis. Presumably, the risk of radiation-induced thyroid cancer should be higher in those adults who were younger at exposure than in those who were elder. That is why age at exposure has also to be taken into account. In our work, we considered both age at the time of diagnosis and age at the time of the Chernobyl accident. This approach allowed demonstration of an extraordinarily high vulnerability of the youngest group aged 0–4 years at exposure and also investigation of radiation-related thyroid carcinogenesis in exposed adults.

The decrease in incidence rate ratios observed in 2006 in all groups of age at the time of accident may imply that the peak of excess of radiation-induced thyroid cancer is already passed. This statement, however, should be taken cautiously because similar annual data presented by

Tronko et al. (2009) for persons aged 0–14 and 15–18 years at the time of the Chernobyl accident do not comply with our observations.

Conclusions

It should be stressed that for the first time, a comparative analysis of thyroid cancer incidence in Ukraine after the Chernobyl accident was performed in a cohort that is almost as large as the general population. The finding of a probable excess of radiation-induced thyroid cancer cases in adults, especially in females, may be due just to the adequately high study power. From the international literature, it is well known that the excess thyroid cancer rates due to exposure to radioactive iodine tends to increase with time for more than 20 years, mainly for those exposed as young children. In the present ecological study, it was difficult, however, to evaluate the potential contribution of an increased screening of the thyroid glands, which may partly have contributed to the observed increase in thyroid cancer cases, for example because of a more frequent use of ultrasound devices in medical diagnostics. Note, however, that we performed such evaluation of the screening effect in young age-groups.

It should be acknowledged that our investigation was not free from ecological biases and limitations. Precise estimation of radiation risks requires thoroughly designed cohort or case–control studies including detailed information about doses and confounding factors (both endogenous and exogenous) that might also affect the investigated thyroid cancer incidence, in addition to ionizing radiation.

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REVIEW

Cancer consequences of the Chernobyl accident: 20 years on

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Abstract

26 April 2006 marks the 20th anniversary of the Chernobyl accident. On this occasion, the World Health Organization (WHO), within the UN Chernobyl Forum initiative, convened an Expert Group to evaluate the health impacts of Chernobyl. This paper summarises the findings relating to cancer. A dramatic increase in the incidence of thyroid cancer has been observed among those exposed to radioactive iodines in childhood and adolescence in the most contaminated territories. Iodine deficiency may have increased the risk of developing thyroid cancer following exposure to radioactive iodines, while prolonged stable iodine supplementation in the years after exposure may reduce this risk. Although increases in rates of other cancers have been reported, much of these increases appear to be due to other factors, including improvements in registration, reporting and diagnosis. Studies are few, however, and have methodological limitations. Further, because most radiation-related solid cancers continue to occur decades after exposure and because only 20 years have passed since the accident, it is too early to evaluate the full radiological impact of the accident. Apart from the large increase in thyroid cancer incidence in young people, there are at present no clearly demonstrated radiation-related increases in cancer risk. This should not, however, be interpreted to mean that no increase has in fact occurred: based on the experience of other populations exposed to ionising radiation, a small increase in the relative risk of cancer is expected, even at the low to moderate doses received. Although it is expected that epidemiological studies will have difficulty identifying such a risk, it may nevertheless translate into a substantial number of radiation-related cancer cases in the future, given the very large number of individuals exposed.

1. Introduction

26 April 2006 marks the 20th anniversary of the accident at the Chernobyl nuclear plant in northern Ukraine, the largest nuclear accident in history. As a result of the accident about five million people were exposed to radioactive contamination in Belarus, the Russian Federation and Ukraine. The knowledge gained in the last 20 years provides valuable information on the

effects of environmental and occupational radiation exposure and will contribute to determining how best to respond to any future accidents of this nature.

2. Methods

In 2003, the WHO convened an Expert Group on Health (EGH) within the UN Chernobyl Forum, an initiative supported by eight UN organisations. After three years of work, the WHO-EGH produced a comprehensive technical report, 'Health effects of the Chernobyl accident and special health care programmes', including detailed critical reviews of published, scientifically valid studies of thyroid cancer, leukaemia and other cancers, as well as non-cancer outcomes (UN Chernobyl Forum 2006). The EGH gave little, if any, weight to anecdotal observations. The present paper, focused on radiation dosimetry and epidemiology, summarises the findings related to cancer, the main long-term effect expected as a result of radiation exposure (UNSCEAR 2000, US NRC 2006).

3. Results

3.1. Sources and levels of radiation dose

The greatest sources of radiation dose from Chernobyl were, at different time periods, intake of short-lived radioactive iodines (particularly ^{131}I), external exposure from radionuclides deposited on the ground (particularly ^{95}Zr + ^{95}Nb, ^{103}Ru, ^{106}Ru, ^{132}Te + ^{132}I, ^{140}Ba + ^{140}La, ^{141}Ce and ^{144}Ce) and ingestion of radioactive caesiums (particularly ^{134}Cs and ^{137}Cs).

Three major groups of people were exposed to and, in some cases, are still being exposed to radioactive contamination:

1. *Workers (liquidators, or emergency and recovery operations workers).* Those individuals who were involved in emergency response, containment, clean-up and associated activities at the Chernobyl site and in the contaminated areas, commonly referred to as liquidators. This group consists of approximately 600 000 individuals, of whom about 240 000 worked in 1986 and 1987, when doses were highest, at the reactor site and the surrounding 30 km zone (Cardis *et al* 1996).
2. *Inhabitants who were evacuated or relocated from contaminated areas.* In the months following the accident about 116 000 people were evacuated from areas surrounding the reactor in Belarus, the Russian Federation and Ukraine. A further 220 000 people were relocated after 1986.
3. *Inhabitants of contaminated areas who were not evacuated.* About 5 million people continue to live in areas of Belarus, Ukraine and Russia that were contaminated by the accident.

Table 1 presents a summary of the number of persons exposed and the levels of doses received in these population groups. Residents of contaminated areas include residents of strict control zones (where strict measures to monitor and decrease annual whole body doses continue to be implemented) and residents of less contaminated areas.

The liquidators were mainly exposed to external γ- and β-radiation. Internal exposure due to ingestion was negligible, though inhaled radioiodines may have contributed to the dose for a small proportion of the liquidators during the first weeks after the accident. In the first few days after the accident, dose-rates were extremely heterogeneous and those liquidators who worked on the industrial site of the Chernobyl Nuclear Power Plant could receive very high doses (up to

Table 1. Estimates of mean effective doses (mSv) for population groups of interest (Cardis *et al* 1996, UNSCEAR 2000).

Population	Approximate size of population	Mean effective dose (mSv)
Liquidators (1986–1987, 30 km zone)	240 000	100
Evacuees of 1986	116 000	33
Persons living in contaminated areas:		
Deposition density of ^{137}Cs > 37 kBq m^{-2}	5200 000[a]	10[b]
Deposition density of ^{137}Cs > 555 kBq m^{-2}[c]	270 000	50[b]

[a] Including approximately 1 900 000 persons from Belarus, 2 000 000 from Russia and 1 300 000 from Ukraine (UNSCEAR 2000).
[b] For the period 1986–2005.
[c] Strict control zones (included in the areas with deposition density >37 kBq m^{-2}).

Table 2. Distribution of doses to clean-up workers as recorded in state Chernobyl registries (UN Chernobyl Forum 2006).

Country and period	Number of clean-up workers	Percentage for whom dose is available	External dose (mSv)			
			Mean	Median	75th (%)	95th (%)
Belarus						
1986–1987	31 000	28	39	20	67	111
1986–1989	63 000	14	43	24	67	119
Russian Federation						
1986	69 000	51	169	194	220	250
1987	53 000	71	92	92	100	208
1988	20 500	83	34	26	45	94
1989	6 000	73	32	30	48	52
1986–1989	148 000	63	107	92	180	240
Ukraine						
1986	98 000	41	185	190	237	326
1987	43 000	72	112	105	142	236
1988	18 000	79	47	33	50	134
1989	11 000	86	35	28	42	107
1986–1989	170 000	56	126	112	192	293

several Sv). In the course of time, due to decay of radionuclides and decontamination activities, dose-rates dropped significantly. This, together with the implementation (from the end of May 1986) of practices to limit exposure, resulted in doses that were generally below permissible levels (250 mSv in 1986; 50–100 mSv in 1987, depending on the work). The distribution of doses available in the State Chernobyl Registries is shown in table 2. The average recorded dose for the liquidators who worked on the reactor site and 30 km zone in 1986–87 is about 100 mSv (table 1), with few individual doses over 250 mSv.

The effective dose estimates for individuals in the general population accumulated over the 20 years following the accident (1986–2005) range from a few mSv to some hundred mSv depending on location, age and lifestyle factors, such as diet, or time spent outdoors. These doses are mainly due to external exposure from a mixture of deposited radionuclides, as well as to internal exposure from intake of ^{134}Cs and ^{137}Cs (UNSCEAR 2000). The mean effective dose accumulated up to 2005 among residents in the strict control zones (with ^{137}Cs deposition density of 555 kBq m^{-2} or more) is of the order of 50 mSv, while in less contaminated areas

Table 3. Estimates of thyroid doses (Goulko *et al* 1996, Likhtarov *et al* 2005, Minenko 2000, UNSCEAR 2000).

		Mean thyroid dose (Gy)		
Population	Size of population	0–7 years	Adults	Total
Evacuees of 1986, including	116 131	1.82	0.29	0.48
villages, Belarus	24 725	3.10	0.68	1.00
Pripyat town	49 360	0.97	0.07	0.17
villages, Ukraine	28 455	2.70	0.40	0.65
Belarus				
Entire country	10 000 000	0.15	0.04	0.05
Gomel region	1 680 000	0.61	0.15	0.22
Ukraine				
Entire country	55 000 000	—	—	0.01
Region around Chernobyl NPP	500 000	—	—	0.38
Kiev city	3 000 000	—	—	0.04
Russian Federation				
Entire country	150 000 000	—	—	0.002
Bryansk region	1 457 500	0.16	0.026	0.04
Kaluga, Orel, Tula regions	4 000 000	—	—	0.01

it is of the order of 10 mSv (table 1). For comparison, the average effective dose from natural background radiation, excluding radon, to an average person is about 1 mSv/year (UNSCEAR 2000), or about 70–80 mSv over a lifetime.

The highest organ-specific dose was to the thyroid gland, primarily from ingestion of milk contaminated with radioactive iodines, particularly ^{131}I. However, there are other sources of exposure resulting from the Chernobyl accident that contribute to thyroid dose, including intake of short-lived radioiodines (^{132}I, ^{133}I and ^{135}I) and radiotelluriums (^{131}Te and ^{132}Te), external irradiation from radionuclides deposited on the ground and ingestion of ^{134}Cs and ^{137}Cs. These represent, for most individuals, only a small percentage of the thyroid dose due to ^{131}I.

The estimation of thyroid doses from ^{131}I is mainly based on the 350 000 direct thyroid exposure-rate measurements made among residents of Belarus, Ukraine and the Russian Federation, within a few weeks of the accident (UNSCEAR 2000, Gavrilin *et al* 1999, Likhtarov *et al* 2005, Zvonova and Balonov 1993). A wide range of thyroid doses was received by the inhabitants of the contaminated areas in the three affected countries. Doses varied with age at the time of the accident, level of ground contamination and rate and source of milk consumption. Reported individual thyroid doses ranged up to several tens of Gy, while average doses range from a few tens of mGy to several Gy (table 3).

Intake of stable iodine tablets during the first 6–30 h after the accident reduced the thyroid dose of the residents of Pripyat by a factor of six to seven on average (Balonov *et al* 2003, Goulko *et al* 1996). Pripyat was the largest city near Chernobyl and close to 50 000 residents were evacuated within 40 h of the accident.

3.2. Epidemiological studies

To date, most of the published studies of health consequences have been of the ecological type, where information on dose and health outcomes (and occasionally on potential confounders) is available only at the group or population level. This type of study can be subject to potential bias, in particular the ecological fallacy (the failure of group level data to properly

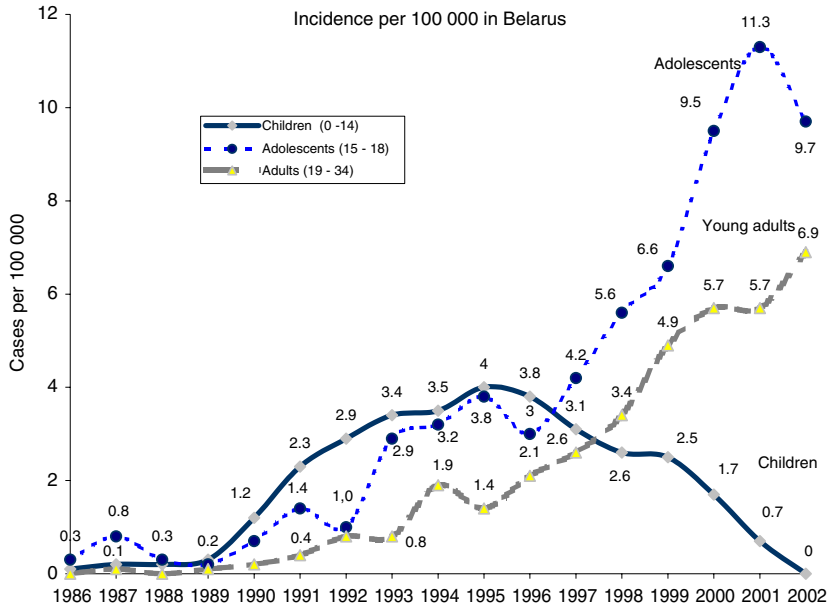

Figure 1. Annual incidence of childhood, adolescent and adult thyroid cancer in Belarus (courtesy of Yu E Demidchik).

(This figure is in colour only in the electronic version)

reflect individual level associations) (Greenland and Morgenstern 1989, Piantadosi *et al* 1988). Analytical studies in which information is collected at the individual level, in particular case–control and cohort studies, are therefore important to evaluate the health risks associated with the Chernobyl accident (UNSCEAR 2000).

3.2.1. Thyroid cancer. The main health effect of radiation from the accident observed to date is a dramatic increase in the incidence of thyroid cancer in persons exposed as young people. This increase was observed first in the early 1990s in Belarus and continues until now in the most contaminated areas of Belarus, Ukraine and the Russian Federation (Jacob *et al* 2006, Kazakov *et al* 1992, Stsjazhko *et al* 1995, UNSCEAR 2000). To illustrate this, figure 1 shows the temporal trends of childhood (0–14 years), adolescent (15–18 years) and adult (19–34 years) thyroid cancer in the general population of Belarus following the accident. By 1995, the incidence of childhood thyroid cancer had increased to four per 100 000 per year compared to 0.03–0.05 cases per 100 000 per year prior to the accident. As those who were children at the time of the accident have aged (by 2002, even the very youngest had reached adulthood), the childhood thyroid cancer rates have declined to near zero and parallel increases in the incidence of thyroid cancer in adolescents and slightly later in young adults have been seen.

The number of thyroid cancer cases diagnosed in Belarus, Ukraine and in the four most contaminated regions of Russia during 1986–2002 among those who were children (<15) or adolescents (15–17) at the time of the Chernobyl accident is presented in table 4. Altogether close to 5000 cases were observed in the three countries. Of these, 15 are known to have been fatal up to now.

At the time of the Chernobyl accident, it was widely held that radioactive iodines were much less carcinogenic than external photon exposure, as little or no experience of the effects

Table 4. Number of cases of thyroid cancer diagnosed between 1986 and 2002, by country and age at exposure.

	Number of cases			
Age at exposure (years)	Belarus[a]	Russian Federation (4 most contaminated regions)[b]	Ukraine[c]	Total
<15	1711	349	1 762	3822
15–17	299	134	582	1015
Total	2010	483	2 344	4837
Population aged less than 15 years in 1986	2300 000	1100 000	11 000 000	14 400 000

[a] Cancer Registry of Belarus, 2006.
[b] Cancer subregistry of the Russian National Medical and Dosimetric Registry, 2006.
[c] Cancer Registry of Ukraine, 2006.

of the isotopes of iodine on the child's thyroid was available (Baverstock and Cardis 1996). Information on radiation induced thyroid cancer came from studies of populations exposed to external radiation, mainly the atomic bomb survivors and patients who received therapeutic exposures in childhood and infancy. The estimate of risk for persons exposed to x- or γ-radiation before age 15, from a combined analysis of these studies (Ron *et al* 1995), is shown in table 5. A number of epidemiological studies of thyroid cancer following exposure to radioactive iodines from the Chernobyl accident have been reported both in the most contaminated countries and in other European countries (UNSCEAR 2000). The most recent and informative studies of persons exposed in childhood and adolescence are also summarised in table 5. The excess relative risks (ERRs) derived in the case–control and cohort studies are all similar, though slightly lower than the estimate from studies of external radiation. The risk estimate from the ecological study is, on the other hand, higher but statistically compatible with that from studies of external radiation. The reasons for the difference in risk estimates for the two study designs are not yet clear, although uncertainties in dose estimates may be partly responsible.

Based on many decades of follow-up of studies of populations exposed to external radiation (Ron *et al* 1995), it is expected that Chernobyl-related thyroid cancers will continue to occur for many more years, although the long-term magnitude of risk cannot yet be quantified.

There is some indication that iodine deficiency at the time of exposure may increase the risk of developing thyroid cancer among persons exposed to ^{131}I as children (Cardis *et al* 2005a, Shakhtarin *et al* 2003). Conversely, prolonged stable iodine supplementation in the years after exposure may reduce this risk (Cardis *et al* 2005a). Further studies are needed to replicate these findings.

Papillary cancer is the primary pathological type of thyroid cancer found in those exposed as children and adolescents to fallout from the Chernobyl accident. The biology of radiation-induced thyroid cancer does not appear to be fundamentally different from that seen in non-irradiated populations, although a slightly greater percentage of radiation-induced thyroid cancers appear to be papillary in nature (Williams *et al* 2004). Possible differences in the molecular biology of the tumours, particularly with regard to *RET/PTC* rearrangements and *BRAF* mutations, are unclear at this time (Detours *et al* 2005, Powell *et al* 2005).

While the increased risk of thyroid cancer in those exposed in childhood and adolescence is well demonstrated, the effect of exposure on adults remains unclear. In the only study that has evaluated the risk for adults living in the contaminated areas (Ivanov *et al* 2003a), no

Table 5. Summary of the case–control and cohort studies, and of the most recent ecological study of thyroid cancer following the Chernobyl accident: comparison with a combined analysis of data on populations with external exposures.

Reference	Type of study	Country/ Region	Number of cases (ascertainment period)	Number of controls/size of study population	Type of thyroid dose	ERR at 1 Gy (95% CI)
Ron *et al* (1995)	Pooled analyses of 5 cohort studies	International	436	119 387	Individual doses from external exposure (x-ray, neutrons)	7.7 (2.1–28.7)
Astakhova *et al* (1998)	Case–control study (population based)	Belarus	107 (1988–92)	214	Individualised doses from ^{131}I (inferred from estimated mean adult thyroid dose in the village of residence, accounting for age and place of residence)	ERR: N.A[a] OR[b] $\geqslant$ 1 Gy versus <0.3 Gy: 5.0 (1.5–16.7) to 5.8 (2.0–17.3)
Davis *et al* (2004)	Case–control study (population based)	Russia (Bryansk)	26 (1991–1997)	52	Individual reconstruction of doses from ^{131}I	N.A
Cardis *et al* (2005a)	Case–control study (population based)	Belarus (Gomel, Mogilev), Russia (Bryansk, Kaluga, Orel, Tula)	276 (1992–1998)	1300	Individual reconstruction of doses from ^{131}I, external irradiation, intake of short-lived radioiodines and long-lived radionuclides	4.5 (2.1–8.5) to 7.4 (3.1–16.3)
Jacob *et al* (2006)	Ecologic	Belarus and Ukraine	1089 (1990–2001)	1620 000	Age–gender –settlement specific doses due to ^{131}I exposure derived from measurements of thyroid activity	18.9 (11.1–26.7)
Tronko *et al* (2006)	Cohort (screened)	Ukraine	45 (1998–2000)	13 127	Individual reconstruction of doses from ^{131}I based on measurements of thyroid activity	Approximately 5

[a] N.A.: not available.
[b] OR: odds ratio.

dose–response relationship was found. No association with radiation dose was observed in studies of Estonian, Latvian and Russian liquidators (Rahu *et al* 2006, Ivanov *et al* 2002).

3.2.2. Leukaemia. Leukaemia (excluding chronic lymphocytic leukaemia) has been associated with exposure to ionising radiation in a number of populations, including atomic bomb survivors, patients treated with radiotherapy and populations exposed occupationally in medicine and the nuclear industry (UNSCEAR 2000). Increases in leukaemia risk appear within 2 to 5 years after exposure and the ERR per unit of dose (particularly in children) is one of the highest among all radiation-induced cancers (UNSCEAR 2000, US NRC 2006). Leukaemia incidence and mortality are, therefore, often considered 'markers' of radiation risks in exposed populations.

It has been suggested in ecological studies in Europe, particularly in Greece (Petridou *et al* 1996), that *in utero* radiation exposure from Chernobyl may increase the risk of infant leukaemia. These results have not been confirmed in a similar study in Germany (Steiner *et al* 1998) and results of studies in Belarus (Ivanov *et al* 1998) and Ukraine (Noshchenko *et al* 2001), where this has also been investigated, are not consistent. Because the studies had low statistical power and the exposure measures were crude, the association between leukaemia and *in utero* exposure is still unclear.

Several ecological studies have examined the association between leukaemia risk and exposure to radiation from the Chernobyl accident in childhood, including the European Childhood Leukaemia–Lymphoma Study (ECLIS), the largest and most comprehensive study to date (Parkin *et al* 1993, 1996), and national incidence studies in Belarus (Gapanovich *et al* 2001, Ivanov *et al* 1993) and Russia (Ivanov and Tsyb 2002, Ivanov *et al* 2003b). The ECLIS study found no evidence of a radiation-related increase in the incidence of leukaemia in Europe in the first five years after the accident. The national studies (including those in Belarus and the Russian Federation) do not, in general, provide evidence for an increase in the incidence of childhood leukaemia. None of these studies, however, is sufficiently sensitive to detect small changes in the incidence of rare diseases such as childhood leukaemia and all are subject to methodological problems that may limit the interpretation of the findings.

Only two case–control studies of childhood leukaemia have been published to date (Noshchenko *et al* 2002, Davis *et al* 2005). A significant association between leukaemia risk and radiation dose to the bone marrow was found in Ukraine but results are difficult to interpret due to problems in the selection and comparability of controls in Ukraine. No significant increase was seen in Belarus or Russia.

Thus, the current information is scant and conclusions cannot be drawn about possible increases in childhood leukaemia following the Chernobyl accident.

The results of studies of leukaemia risk among adults, conducted both among persons residing in contaminated areas and among liquidators, are equally inconclusive. The studies of leukaemia risk among adult populations living in highly contaminated areas are ecological in nature and generally indicate an increase in leukaemia incidence over time, that does not appear to be related to level of contamination (Bebeshko *et al* 1997, Ivanov *et al* 1997, Prisyazhniuk *et al* 1995). Small studies of Estonian and Russian liquidators provide little information about risks (Rahu *et al* 1997, Shantyr *et al* 1997, Tukov and Dzagoeva 1993, Rahu *et al* 2006), while an apparent increase in incidence of leukaemia in a large cohort of Ukrainian liquidators (Buzunov *et al* 1996) is not related to dose. An approximately twofold increased risk is reported however in a very large cohort of liquidators in Russia with registered radiation doses between 150 and 300 mSv (Ivanov *et al* 2003c). Dose estimates are quite uncertain in these studies. Ongoing case–control studies of liquidators with individual dose estimates are expected to provide additional information on the magnitude of a possible increased risk of leukaemia.

3.2.3. Solid cancers other than thyroid cancer. Although ionising radiation has been shown to increase the risk of cancers at many sites, data from Chernobyl on cancers other than thyroid cancer are very sparse (UNSCEAR 2000).

No significant increase in the incidence of solid cancers (defined as all cancers excluding haematological malignancies) was seen in a cohort of over 55 000 Russian liquidators (Ivanov *et al* 2004) or among.residents of the contaminated region of Kaluga in Russia (Ivanov *et al* 1997).

Analyses of rates of breast cancer among subjects included in the Ukrainian Chernobyl registry indicated a significantly increased incidence compared to the general population (Prysyazhnyuk *et al* 2002). Increases in the incidence of breast cancer over time were also reported in the Mogilev region of Belarus (Ostapenko *et al* 1998). Both of these reports are difficult to interpret, as no information about radiation dose level was available. A more detailed ecological study was therefore conducted to describe the spatial and temporal trends in breast cancer incidence in Belarus and Ukraine (Pukkala *et al* 2006). A large increase in breast cancer incidence was found in all areas of Belarus and Ukraine, reflecting improvements in cancer diagnosis and registration. A significant increase in risk was also observed during the period 1997–2001, based on a relatively small number of cases, in the districts with highest average dose levels compared to the least exposed districts. The magnitude of this increase is greater, however, than would be expected based on current risk estimates (US NRC 2006). Due to the public health importance of breast cancer, these findings warrant further investigation.

Increases in rates of other cancers, including cancers of the bladder and kidney, have also been reported (reviewed UN Chernobyl Forum, 2006). Because of various limitations (including small numbers of cases and/or controls, inadequate information on doses and/or on epidemiological methods and lack of information on other common risk factors for these diseases), it is difficult to judge the scientific merits of the findings.

4. Discussion

The study of the consequences of the Chernobyl accident has provided important information concerning the magnitude of the risk, and the biology of thyroid cancer following exposure to radioactive iodines in childhood and adolescence.

There remains, however, a lack of evidence of any clearly demonstrated effect of Chernobyl radiation exposures on the risk of leukaemia or solid cancers other than thyroid cancer. There have been reports of an elevated incidence of all solid cancers combined, as well as of specific cancers in Belarus, the Russian Federation and Ukraine, but much of the increase appears to be due to other factors, including improvements in diagnosis, reporting and registration. An increase in the incidence of breast cancer in the most heavily contaminated districts suggests a possible relation to radiation exposure. Recent studies suggest a doubling of leukaemia risk among Chernobyl liquidators. Both of these findings need confirmation in well designed analytical epidemiological studies with careful reconstruction of individual organ doses.

As noted above, studies of cancer risk other than thyroid are few and most have methodological limitations. Doses to most organs outside the thyroid tended to be low and studies lacked statistical power. Further, it is thought that for most solid cancers the latent period is likely to be longer than for leukaemia or thyroid cancer—of the order of 10–15 years or more (Cardis *et al* 2005b). Because studies of external radiation indicate that radiation-related risks of solid cancers remain elevated throughout life, it is too early to evaluate the full radiological impact of the Chernobyl accident.

The fact that no significant increased cancer risk, apart from thyroid cancer, has been conclusively demonstrated to date among populations most exposed to the Chernobyl accident does not therefore imply that no increase in risk has occurred. Indeed, based on the experience of other populations exposed to ionising radiation, it is expected that the low to moderate doses received will have led to a small increase in the relative risk of cancer. Given the large number of individuals exposed, the absolute number of cancer cases caused by a small increase in the relative risk could be substantial, particularly in the future.

The question of estimating the number of cancer cases which could occur due to the Chernobyl accident is important for public health planning purposes. At present, given the lack of demonstrated increases and the relatively short follow-up for solid cancers, any such estimation must be based on risk estimates derived from other populations exposed to radiation, most notably the atomic bomb survivors. This implies a number of uncertainties. Major uncertainties relate to the choice of models used for transfer of risk between populations with different background cancer rates, for projection of risk over time and for extrapolation of risks following primarily external high dose and high dose-rate exposure to very low dose and low dose-rate exposures involving a mixture of external and internal radiation. Unfortunately, these problems limit the accuracy and precision of such projections.

In 1996, Cardis *et al* published predictions of the health effects of Chernobyl radiation, derived from models of radiation-associated risk from epidemiological studies of other populations exposed to radiation, mainly members of the Life Span Study (LSS) of Japanese atomic bomb survivors. The predicted lifetime excess of cancer and leukaemia deaths due to radiation from the Chernobyl accident was of the order of 4000 for liquidators, evacuees and residents of the strict control zones. A further 5000 cancer deaths were predicted among residents of other contaminated areas, for a total of about 9000 deaths among the most exposed persons in Belarus, the Russian Federation and Ukraine. This number is only an indication of the likely impact of the accident and should not be taken at face value because of the important uncertainties listed above. Although the absolute number of predicted deaths is large, it represents only a small fraction (about 1%) of the total number of cancers expected in these populations from other causes.

If these predictions are correct, therefore, it is expected that epidemiological studies will have limited statistical power to detect small increases of risk against much larger background rates of cancer. Further, the absence of high quality disease registers in many of the contaminated regions at the time of the accident, recent changes in the longevity of the populations in the affected countries (both in contaminated and uncontaminated regions) and the absence of individual dose estimates for the majority of exposed persons make it difficult to conduct informative epidemiological studies. On the other hand, well designed studies of carefully selected populations (such as the liquidators) and endpoints (in particular leukaemia, as well as breast cancer in young women) will facilitate the detection of a wider spectrum of health effects and possibly provide important additional information about radiation risks.

5. Conclusion

Today, nearly 20 years after the Chernobyl accident, the large increase in thyroid cancer incidence among those exposed in childhood and adolescence continues; fortunately, few of these have been fatal. In contrast, at this time, no clearly demonstrated increase in the incidence of other cancers can be attributed to radiation exposure from the accident.

Of course, the absence of a demonstrated increase in total cancer risk is not proof that no increase has, in fact, occurred. Based on the experience of atomic bomb survivors and of populations with medical and occupational exposures to ionising radiation, a small increase

in the relative risk of cancer is expected, even at the low to moderate doses received. Given the very large number of individuals exposed, even a small increase in the relative risk would result in a substantial number of radiation-related cancer cases in the future. In the coming years, careful studies of selected populations and health outcomes are needed in order to study the full effects of the accident and compare them to predictions.

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2 РОЗРОБКА ДИЗАЙНУ ДОСЛІДЖЕННЯ ТА ОБГРУНТУВАННЯ СКЛАДОВИХ ДОКАЗОВОГО АНАЛІТИЧНОГО ДОСЛІДЖЕННЯ

У розділі визначено найважливіші складові якісного аналітичного епідеміологічного дослідження для забезпечення доказовості отриманих результатів, в тому числі: забезпечення адекватної потужності дослідження з урахуванням відповідних характеристик обраної досліджуваної когорти, дизайну дослідження (когортний або випадок-контроль, чи випадок-когорта); ідентифікація випадків захворювання у повному обсязі і з гарантованою верифікацією діагнозів. використання альтернативних джерел інформації про випадки;; незалежна діагностична експертиза, бажано із залученням міжнародних експертів; вибір адекватного методу дозиметрії, який відповідає характеру опромінення, та відповідним критеріям якості.

Когорту учасників ЛНА для дослідження лейкемії було сформовано за даними Державного реєстру України осіб, кі постраждвли внаслідок Чоорнобильської катастрофи (ДРУ), який було попередньо протестовано щодо наявності достатньої персоналізованої інформації для формування когорти учасників ліквідації наслідків аварії згідно заданим критеріям, простеження членів когорти і зіставлення з іншими інформаційними масивами (базами даних). В досліджувану когорту було включено 110 645 зареєстрованих ліквідаторів чоловічої статі, які мешкали на час реєстрації в 5 областях України і м. Київ, що склало приблизно 48% всіх зареєстрованих. Для дослідження було обрано дизайн випадок-контроль в когорті учасників

ліквідації наслідків аварії (гніздове (вкладене) випадок-контроль дослідження).

Статистичну потужність дослідження було обраховано з використанням статистичного пакету (EPICURE). В дослідженні лейкемії та споріднених захворювань було визначено, що розмір досліджуваної когорти, запланований період спостереження (15 років і більше) та можливий рівень відносної біологічної ефективності опромінення внаслідок Чорнобильської катастрофи від 0,5 до 1,0, порівняно із когортою опромінених унаслідок ядерного бомбування в Японії, забезпечать прийнятний рівень статистичної потужності (не менший за 80%), за підбору 5 контролів для кожного випадку.

Якщо реальний ризик буде нижчим за 50%, статистична потужність не перевищить 75%.

Пізніше для дослідження раку щитоподібної залози когорту було збільшено за рахунок ліквідаторів чоловічої статі, які мешкали в Донецькій області, зі збереженням необхідної потужності дослідження. Розширена когорта включала 150 813 осіб.

На етапі планування досліджень було визначено джерела і способи ідентифікації випадків захворювання, методи дозиметрії для ретроспективного відновлення дози опромінення цільових органів, а також підходи до статистичного аналізу даних і оцінки ризиків.

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The Ukrainian-American Study of Leukemia and Related Disorders among Chornobyl Cleanup Workers from Ukraine: I. Study Methods

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There are relatively few data on the risk of leukemia among those exposed to external radiation during cleanup operations after the Chornobyl nuclear accident, and results have not been consistent. To investigate this further, we assembled a cohort of 110,645 male cleanup workers from Ukraine and identified cases of leukemia occurring during the period 1986 to 2000. Detailed interviews were conducted and individual bone marrow doses estimated using a new time-and-motion method known as RADRUE described in companion paper II. For the initial analyses we used a nested case-control approach with a minimum of five controls per case, matched for year of birth, oblast (region) of registration, and residence. All identified cases were reviewed by an international panel of experts; 87 of 111 were confirmed. The dose–response analysis and results are given in companion paper III. As background, we describe herein the design, procedures, outcome of case finding and confirmation, control selection, dose estimation and interviewing of subjects.

INTRODUCTION

After the accident at the Chornobyl (Chernobyl) nuclear power plant on April 26, 1986, hundreds of thousands of people were sent to the site of the plant or the 30-km zone surrounding it to help with decontamination, sarcophagus construction, and other cleanup operations, including evacuation of civilians from the 30-km zone. These workers are generally known as cleanup workers or liquidators [because of language in a government order charging them with ''liquidating'' the consequences (ill effects) of the accident]. Sent to the reactor site mainly from 1986 through 1990, usually for a period of about 2 weeks, the cleanup workers were exposed primarily to external radiation from γ-ray-emitting radionuclides, with those workers sent earliest receiving the highest doses. Estimates derived from national Chornobyl registry data in Ukraine, Belarus and the Russian Federation indicated a mean dose from external radiation of 144 mGy in 1986, 90 mGy in 1987, and 36 mGy in 1988–1989 (*1*). A later analysis (*2*) has updated these estimates: for Ukraine, a mean of 185 mGy in 1986, 112 mGy in 1987, and 47 mGy in 1988; for Russia, 169 mGy, 92 mGy and 34 mGy; for Belarus, 60 mGy, 28 mGy and 20 mGy.

Studies of cancer among cleanup workers so far have focused on the risk of leukemia, given the relatively short latency and sensitivity to radiation [excepting chronic lymphocytic leukemia (CLL), which has generally been regarded as non-radiosensitive (*3*)]. Results from studies to date are somewhat equivocal due to methodological limitations but seem to point to a possible raised risk of leukemia in this population. Until recently, most of the epidemiological research has been based on national Chornobyl registries, particularly the National Medical and Dosimetric Registry in Russia, for example, refs. (*4, 5*). The strongest of the registry-based studies from a methodological point of view (*5*) used internal comparisons based on individual dose estimates obtained from the Russian Registry and morphologically confirmed cases. This study, based on 42 non-CLL leukemias diagnosed between 1986 and 1998 in a cohort of 71,870 Russian workers sent to the 30-km zone, found a standardized incidence ratio of 2.2 [90% confidence interval (CI): 1.3, 3.7] comparing those exposed at higher doses (150–300 mGy) to those with doses <150 mGy (duration of exposure not stated). The excess

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relative risk (ERR) at 1 Gy was estimated to be 6.7 (90% CI: 0.8, 23.5), while the relative risk estimate was 2.2. Most other registry-based studies in Russia relied on external comparisons to general population rates, although the cleanup workers received a higher level of medical surveillance, raising the possibility of more complete case ascertainment, which might bias the risk estimate upward for cleanup workers.

In Ukraine, a survey of 174,812 cleanup workers identified through the State Registry of Ukraine (SRU) (*6*) investigated the health status of this group, the majority of whom (77%) were exposed in 1986–1987. The data were analyzed using the year on site at Chornobyl as a surrogate for exposure level. The average rate of leukemia from 1987 through 1992 as calculated from the number of cases reported in the Registry was 13.4/100,000 person-years among those employed in cleanup work in 1986 and 7.0 per 100,000 person-years among those employed in 1987.

Two other studies using case-control methodology have been reported that were also based on the Registry of Russian clean-up workers (*7, 8*). The earlier of these (*7*) was based on a cohort of 155,680 male Russian cleanup workers observed from 1986 to 1993, among whom 34 total leukemias were found, of which 10 were CLL. The estimated ERRs per Gy comparing the occurrence of leukemia in liquidators with the Russian national rates of leukemia were 0.24 (95% CI: −3.9, 4.4) for all leukemias and 1.67 (95% CI: −5.9, 9.2) for leukemia excluding CLL. An analysis of workers in the 30-km zone in 1986–1987 when exposures were highest found counterintuitive results: lower ERRs than for all workers and hence no apparent positive trend with increasing dose. Moreover, a case-control analysis nested in the cohort showed no association with dose.

The later study, with follow-up to 1995 (*8*), included a total of 162,684 Russian cleanup workers from the same Registry. After allowing for a 2-year latent period, 41 leukemia cases were diagnosed, of which 13 were CLL. The matched case-control analysis, using the same covariates as the earlier study, found no difference in risk. A second analysis using all of the non-cases in the cohort yielded an estimated ERR per Gy of 1.33 (95% CI: −6.3, 8.9) for all leukemia and 15.59 (95% CI: −24.9, 56.1) for leukemia excluding CLL, but again, the earliest workers on site who appeared to receive the highest doses showed smaller ERRs (i.e., no positive trend with time-based dose estimates).

Among the limitations of both these studies are the use of officially assigned doses whose accuracy has been questioned and the lack of diagnostic confirmation by an independent hematological review panel. Particularly disturbing are the discrepant results from two studies using essentially the same cases drawn from the same base population.

The present nested case-control study is based on a large cohort of 110,645 male cleanup workers from Ukraine who participated in recovery operations in 1986–1990. Follow-up through the year 2000 has yielded a total of 87 confirmed leukemia cases, of which fully 49 were CLL (see companion paper III for further discussion on the relative proportion of CLL to non-CLL cases). The increased statistical power from the case total, higher than that of earlier studies, leads to a more precise evaluation of the possible increased risk of leukemia among Chornobyl liquidators, with doses estimated based on extensive questionnaire data evaluated by dosimetric experts. This paper describes in detail the design, objectives and methods of the study. Two companion papers present the dosimetric aspects of the study (*9*) and the statistical analyses and results (*10*).

SUBJECTS AND METHODS

Study Objectives

The study's main objectives were (1) to test the hypothesis that exposure to radiation during cleanup operations after the Chornobyl accident led to an increase in leukemia among male cleanup workers from Ukraine, (2) to determine the radiation dose–response relationship, (3) to identify any factors (e.g. age) that modify the risk from radiation exposure, and (4) to compare the magnitude of the risk relative to that observed among atomic bomb survivors who experienced essentially instantaneous radiation exposure. Additional objectives were to identify cases of multiple myeloma (MM), for which radiation is a possible risk factor (*11*), and myelodysplastic syndromes (MDS), aggressive forms of which frequently progress into acute myeloid leukemia (*12, 13*). In both instances, however, the numbers were expected to be relatively small.

Overview of Design

Guided by a 2-year feasibility study (*14*), we conducted a nested case-control study of ionizing radiation and leukemia in a cohort of 110,645 male Ukrainian cleanup workers (the number of female cleanup workers being considered too small to be sufficiently informative). The cohort was restricted to cleanup workers (liquidators) registered in the State Registry of Ukraine (SRU) who were resident in Kyiv City or in one of five oblasts (major civil divisions) that comprise the study area (Cherkasy, Chernihiv, Dnipropetrovsk, Kharkiv and Kyiv). The areas were chosen for their large population of liquidators, accessibility to Kyiv City, anticipated cooperation from local medical personnel, and expectation of better recovery of clinical and biological materials on cases. The study was carried out in a 4-year period, 2001–2004, and was focused on the identification and validation of cases of leukemia that occurred between 1986 and 2000, together with age- and oblast-matched controls, alive and free from the diseases under study. Doses to the bone marrow were estimated using a new time-and-motion method called RADRUE (Realistic Analytical Dose Reconstruction with Uncertainty Estimate), which relies on information obtained in a detailed dosimetry interview along with measurements of exposure rate made at various points at and around the reactor site (*2*). Study procedures were recorded in a detailed Operations Manual.

The protocol for the study was approved by the Institutional Review Boards of the U.S. National Cancer Institute (NCI) and the Research Center for Radiation Medicine (RCRM) in Ukraine. All participants gave written informed consent. A Leukemia Advisory Group comprised of leading experts in biostatistics, hematology, epidemiology and dosimetry was created by NCI and provided continuing oversight.

Creation of the Cohort

The study cohort was formed on the basis of data available in the SRU, an official register established in 1986 and supervised by the Ministry of Health of Ukraine. Its main purpose is to monitor those affected by the Chornobyl accident to reveal health effects and make decisions about the provision of medical care and social security. The Registry covers over

TABLE 1
Age Distribution of the Cohort Members in Comparison with all Cleanup Workers Registered at the SRU (State Registry of Ukraine) as of 01.01.2000

Year of birth	Cleanup workers in SRU		Cleanup workers in the Cohort	
	N	Percentage	*N*	Percentage
<1920	154	0.1	119	0.1
1920–1924	365	0.2	255	0.2
1925–1929	2643	1.1	1800	1.6
1930–1934	4825	2.0	2974	2.7
1935–1939	13464	5.6	8810	8.0
1940–1944	15206	6.3	8627	7.8
1945–1949	33004	13.8	15743	14.2
1950–1954	53368	22.2	23950	21.6
1955–1959	59873	25.0	25719	23.2
1960–1964	43920	18.3	17828	16.1
1965–1969	12648	5.3	4537	4.1
≥1970	486	0.2	283	0.3
Total	239956	100	110645	100

200,000 cleanup workers and includes sufficient identifying data to trace and contact potential study subjects.

Eligibility criteria for membership in the study cohort included gender (male; see above), first year of service as a cleanup worker (1986–1990), initial registration as a cleanup worker in one of the study areas, and age when first worked at Chornobyl (under 60, the mandatory retirement age in Ukraine). Subjects were not required to be alive at selection. The assembled cohort of 110,645 Ukrainian cleanup workers represents about 46% of all cleanup workers in Ukraine. Table 1 shows that the age distribution of the study cohort is similar to that of all cleanup workers registered in the SRU. Table 2 shows the geographic distribution of cohort members at the time of registration, with Kyiv City contributing the most cohort members (26.3%) and Cherkasy oblast the least (10.4%).

Case Identification and Validation

As part of the process of ascertaining cases, a provisional computerized registry of leukemia and related hematological disorders was created, based on admission diagnoses, through an intensive search of the files of the oncology, hematology and pathology departments of health care institutions within each study area. A total of 99 ancillary diagnoses, including all lympho- and myeloproliferative diseases, refractory anemias of all types, and various aplastic or hypoplastic anemias, were used to identify all possible cases of leukemia. Only cases who were resident in the study area and who met the age and gender requirements for the study were entered into the Provisional Leukemia Registry, which was ultimately comprised of 37,605 records. The SRU was also searched to identify any cases not found through other sources.

Linkage of the Cohort File with the Provisional Leukemia Registry was accomplished using computerized probabilistic record linkage techniques. Principles of probabilistic record linkage have been reviewed by one of us (*15*). In general, records on two separate files are compared and the probability is estimated that a pair refers to the same person given the identifying information in each record and taking into account duplication and recording errors. Scores above a certain threshold are accepted as true matches.

The initial lists of cases identified as leukemia, MM, MDS or one of the ancillary diagnoses were linked with the cohort file to select those among the cohort who had one or more of the diagnoses of interest. Linkage of the Cohort File with the Provisional Leukemia Registry resulted in the identification of 139 cases of leukemia, MM or MDS that had been diagnosed by Ukrainian hematologists (Group 1). Review of the cases in this group by epidemiologists at RCRM revealed that two were ineligible because they were not liquidators and 27 had to be excluded because a diagnosis of leukemia was not confirmed in hospital records, so the final number from this group was 110. Preliminary screening by the study hematologists at RCRM of the 649 cases in the Registry with one of the ancillary diagnoses that could resemble leukemia (Group 2) identified 22 additional cases. Another seven possible cases were found through review of the 57 subjects in the cohort with leukemia diagnoses that were listed in the SRU but had not been identified through search of the local health care institutions (Group 3). The total of 139 cases from the three groups (110 + 22 + 7) were referred for final case validation directly to an International Hematology Panel consisting of five expert hematologists and hematopathologists (B. Bain, UK; S. Gaiudukova and D. Gluzman, Ukraine; P. McPhedran and L-A. Peterson, U.S.A.).

The validation of diagnoses required the collection of clinical and biological materials for each case for the period from disease onset through follow-up. Accordingly, a search for all available medical records together with peripheral blood smears and slides of bone marrow aspirates was undertaken for each case referred to the International Hematology Panel for review and validation. In addition, other records of biological tissue examination were identified. The search was conducted in the local hospitals, hematology centers, oncology clinics and departments of pathology in the target areas and, in addition, in Kyiv, in the Ukrainian Research Institute of Oncology, the Kyiv Institute of Hematology and Blood Transfusion and the RCRM. Medical records were available for 100% of cases; aspiration smears or biopsy sections were available for 68.3% of cases submitted for review.

The hematology review sessions by the International Hematology Panel, of which there were two, were conducted in Ukraine at the RCRM, each over a period of 4–5 working days. The review process was carried out according to a protocol designed during a preliminary feasibility study (*22*). In brief, each expert on the Panel independently reviewed a clinical abstract of each medical record together with available bone marrow aspiration smears or sections of each case. After the examination of every five cases, each expert expressed his or her opinion regarding diagnosis,

TABLE 2
Distribution of the Cohort Members by Oblast of Residence at the Time of Registration in the SRU

Oblast	Year of cleanup				Total (%)
	1986	1987	1988–1990	Unknown	
Dnipropetrovsk	9296	5560	4142	164	19162 (17.3%)
Kyiv	13604	726	183	6601	21114 (19.1%)
Kharkiv	7794	4993	4276	10	17073 (15.4%)
Cherkasy	5839	2710	2957	40	11546 (10.4%)
Chernihiv	7964	1757	2615	294	12630 (11.4%)
Kyiv City	26397	728	534	1461	29120 (26.3%)
Total	70894	16474	14707	8570	110645

TABLE 3
Distribution of Confirmed Cases by Type

Type[a]	Number of cases confirmed by International Hematology Panel	
AL	19	87 leukemia
CLL	49	
CML	15	
LGL	4	
MDS	6	
MM	8	
Total	101	

[a]AL = acute leukemia NOS ($n = 9$); ALL = acute lymphocytic leukemia ($n = 4$); AML = acute myeloid leukemia ($n = 6$); CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; LGL = large granular lymphocytic leukemia; MDS = myelodysplastic syndrome; MM = multiple myeloma.

together with an estimation of their degree of certainty for the diagnosis. In cases with a disparity of opinion, each case was discussed at length until a consensus diagnosis was reached. Cases were accepted as confirmed cases of leukemia only if there were a clinical history and/or histological materials that supported the consensus diagnosis. Cases for which there was inadequate case documentation because of incomplete medical records or lack of histological evidence were not included in the study. In addition to the cohort cases, 11 negative controls were included randomly in the cases examined.

Acute leukemia and MDS cases were initially identified using the French-American-British system (*16, 17*), with a view to possibly differentiating risk for FAB subtypes. In 2007, the decision was made to change to the WHO system of classification, now the standard in the field (*18*). Multiple myeloma was classified according to the International Staging System proposed by Griepp *et al.* (*19*). Chronic myelogenous leukemia and chronic lymphocytic leukemia were diagnosed using standard criteria. Of the 139 cases referred to the panel, 72.7% were confirmed: 86 of 111 were confirmed as leukemia, eight of 11 as multiple myeloma, and seven of 17 as MDS. After the change to the WHO classification, one case of MDS was reclassified as acute myelogenous leukemia, bringing the total for leukemia to 87 and reducing the total for MDS to six (Table 3). All of the negative control cases were rejected. The Panel was blind to the exposure status of the submitted cases. It should be noted that dosimetry estimates could not be calculated for 16 cases (two ineligible, seven not traced, four refusals, three with incomplete interview data), bringing the final total used in the analysis to 71.

Selection of Controls

Controls for each case (ratio 5:1) were selected randomly from all cohort members initially registered in the same oblast as the cases, free from the diseases under study, and alive and still resident in the study areas at the time the corresponding cases were diagnosed. Other than oblast of registration and residence, the only matching factor used was exact year of birth. To be certain of identifying five appropriate controls, a list of nine controls was compiled for each case. The epidemiologists went through the list in order, taking the first five found to be eligible and willing to participate. Controls ($n = 153$) for cases that were not confirmed by the International Hematology Panel or for whom dose estimates could not be constructed ($n = 16$) were matched to other cases and retained in the analysis as ''extra controls'', although in some cases the match for age was less tight. Ultimately, a total of 501 controls were used in the dose–response analysis, bringing the control:case ratio to close to 7:1 and improving the stability of the risk estimates. [See companion paper III (*10*) for a discussion of response rates among controls.]

TABLE 4
Distribution of the Cohort Members by Oblast of Registration in the SRU and Presence or Absence of Official Dose Records

Oblast	Total with dose record	Without dose record	Total
Dnipropetrovsk	13431	5731	19162
Kyiv	293	20821	21114
Kharkiv	11379	5694	17073
Cherkasy	5005	6541	11546
Chernihiv	5750	6880	12630
Kyiv City	876	28244	29120
Total	36734	73911	110645

Tracing and Recruitment

For both cases and controls, current addresses (or for deceased cases, address at time of death) were ascertained initially through the SRU and then confirmed by asking each liquidator's responsible physician at the oblast level to verify that address. The responsible physician contacted the liquidator by telephone or in person, and the Department of Medical Support of Victims (DMSV) in each oblast wrote to the subject inviting him to come in for an interview with his Chornobyl discharge papers. If, at this stage, the current address was not located, other sources were searched, such as passport bureaus at the oblast level and the rayon (local) or military reservist office, or state administration (a governmental authority that issues certificates to victims of the Chornobyl accident and provides social benefits).

Dosimetry

The task of estimating a dose for all subjects in the study proved to be very challenging. Less than a third of the subjects had official dose estimates recorded in the SRU (Table 4), and the reliability of those official dose estimates is questionable. In part this may be because few of the early liquidators carried any type of dosimeter. Other available sources of dosimetric information, such as the archives of the Ministry of Defense or the dosimetry databases that were acquired during the course of the study, provided information for only a limited number of subjects. Biodosimetry methods such as EPR (electron paramagnetic resonance) on tooth enamel from lost teeth and FISH (fluorescence *in situ* hybridization) on blood samples could be used on only a fraction of subjects and have the disadvantage of measuring total exposure, including components due to medical exposures or to other occupational exposures that cannot be distinguished from exposure at Chornobyl as is possible when such information is gathered by questionnaire, for example. Therefore, it was necessary to develop a universal method of dose estimation that would be (1) applicable to all subjects, whether deceased or alive, and (2) based on information that would be relatively easy to process or to verify.

The new method, known as RADRUE (*9*), was developed in conjunction with an international group of scientists led by Victor Kryuchkov and including experts from Belarus, France, Lithuania, Russia, Ukraine and the U.S. The RADRUE method, which was conceived for this study and a study of cleanup workers from Belarus, the Russian Federation and the Baltic countries conducted by the International Agency for Research on Cancer (IARC), is based on a detailed analysis of the liquidator's activities during cleanup, including all places of work and residence, types of work, transportation, etc. with an indication of dates and duration. This information, obtained during an interview with the liquidator, or with a proxy coworker if the subject was deceased, is combined with data on the radiation dose rates at the locations and dates where the liquidator spent any time to reconstruct a history of doses received during the time the liquidator was involved in cleanup activities. [See companion paper II (*9*) for additional material on the interview.]

In the course of applying the RADRUE method, an expert processes the questionnaire filled in during the interview, reconstructs the itinerary followed by the liquidator, and provides information on the uncertainties associated with the itinerary. A computer program especially developed for the purposes of this study then links the liquidator's itinerary with the radiation environment databases for the 70-km zone around the Chornobyl reactor to calculate his bone marrow dose. The RADRUE computer program can be run in a stochastic mode, thus providing a set of random values of dose that allow for the determination of any parameter of the dose distribution (mean, standard deviation, geometric mean, geometric standard deviation, etc.). Once the itinerary of the liquidator is determined, the calculation of the bone marrow dose and of its uncertainty is fully automatic. Ten thousand random realizations of individual doses were generated for each of the study subjects during the course of the Project.

To reduce uncertainties in the dose estimates, a series of validation studies was undertaken. A more detailed description of the dose reconstruction is presented in a separate paper in this series (*9*).

Proxy Respondents

For deceased cases and controls, interviews were carried out with proxy respondents whenever possible. Two types of proxies were selected for each deceased subject: a spouse or next-of-kin proxy to provide data on demographic factors and medical history, and to propose coworkers who could serve as proxy respondents regarding the deceased liquidator's work history. To obtain the most complete work history possible, in some cases more than one coworker proxy was interviewed. As an indication of the proportion of subjects for whom proxy respondents had to be sought, the final sample used for analysis included 59.2% of cases who were deceased and 7.2% of controls.

Mechanisms to ascertain the current address of a deceased liquidator's next of kin (most probably his spouse) included checking the latest recorded address for the liquidator, reviewing records of the hospital where the case was treated, and contacting military reservist offices, and the state administration at the oblast level responsible for managing the social benefits received by liquidators and, in some cases, their wives.

Coworker proxies were identified either by next-of-kin or employment records for the index subject. To locate coworker proxies, the standard process for tracing liquidators was used.

Interviews and Interviewing Procedures

All traced and consenting cases and controls (or their proxies) were interviewed to obtain detailed information on work history at Chornobyl and on potential confounders or modifiers of radiation risk. The items covered by the questionnaire included demographics, dates and other information about each mission to the 30-km zone, areas where the liquidator lived, dosimetry measurements and radiation protection methods, and a general occupational history. Data were also gathered on non-Chornobyl sources of radiation exposure resulting from previous jobs or medical procedures as well as information on work in hazardous industries or with hazardous chemicals. Finally, a personal and family medical history was collected along with information on smoking and alcohol habits. Thus data were available for analysis of a wide range of potential confounding or effect-modifying variables.

Of note is the fact that all interviewers were former cleanup workers and staff members of the Chornobyl plant, well informed about cleanup activity chronology and familiar with the temporal and spatial characteristics of the radiation fields in the 30-km zone. They were given extensive interviewer training. On an ongoing basis, the senior interviewer provided coordination and quality control over the interviewers through observation of their work and review of questionnaires. In addition, interviewers were asked to rate each interview with respect to completeness and reliability, data that were also of potential utility in the analysis.

All cases and controls (or their proxies) were approached in person or by telephone by a person responsible for the contacts, who followed a standardized approach for inviting the liquidator (or his next of kin) to participate in the study. Subsequent to this personal approach, an invitation letter was sent by the head of the DMSV confirming the invitation to participate in the study. Interviews were conducted in the dispensary departments of the DMSV or, if necessary, in some other convenient location.

Quality Control (QC)

A comprehensive quality control program was developed for the three principal components of the study: epidemiology and data management, hematology and dosimetry. Details of the program were set out in a quality control manual that included the tasks to be monitored, the schedule of monitoring, the person responsible for monitoring and feedback and the method of monitoring. The International Hematology Panel described above is one example of a quality control activity in the area of hematology. Examples of QC activities in other areas include double abstraction of 10% of registration forms from the Provisional Leukemia Registry, complete double-entry of all registration forms, all dosimetry questionnaire data and observation of 10% of all interviews every quarter. All project staff attended a special training course conducted by NCI and WESTAT experts in the field of quality control and were certified in quality control procedures.

Statistical Power

The study has good power (>95%) to test the hypothesis of any radiation effect so long as the true risk is comparable in magnitude to the risk observed in the A-bomb survivors (*20*). If the true risk is 50% lower than that of the A-bomb survivors, the power would be lower at 75%. Power for the case-control study with five controls per case is essentially the same as for the full cohort.

Statistical Analysis

The analytic strategy is described in detail in ref. (*10*). In brief, the primary data analysis consisted of fitting models relating estimates of individual bone marrow dose to the risk of leukemia, using standard conditional logistic regression for matched data. The general form of the model was

$$\text{Risk} = \text{background risk} \times \left\{1.0 + \text{excess relative risk (ERR)} \times \text{dose} \times \exp\left[\sum_i y_i Z_i\right]\right\}, \quad (1)$$

where Z_i represents potential modifying factors with their corresponding parameters y_i. The absorbed doses to bone marrow, lagged by 2 years, were used to estimate the ERR and to evaluate the best mathematical function to describe the dose–response relationship. By adding 1.0 to the ERR, one obtains the relative risk at 1 Gy of radiation.

The PECAN module of the EPICURE (*21*) software was used to fit the models. Maximum likelihood techniques were used for point and interval estimation and for double-sided tests of significance.

DISCUSSION

The study has a number of noteworthy aspects. The cohort from which cases and controls are drawn is large. Deceased liquidators were not excluded from the study, which proved important because of the high death rate. Participation rates, for the proxy respondents for deceased liquidators as well as for subjects themselves, were reasonable, ranging from <70% to 100%, depending on the category (i.e., subject, next-of-kin, coworker). There was strict quality control of the interviews and other elements of the

study. The search for cases was extremely wide-ranging and, to improve identification of leukemia cases, included a list of all potentially related diagnoses, from which 29 were forwarded to the International Hematology Panel and eight additional leukemias were confirmed. Review of diagnoses involved screening of certain groups of cases by hematologists at the local level using international criteria and validation of all the remaining referred cases by a panel of experts from several countries. The approach to estimating radiation dose by means of RADRUE was developed by an international group of dosimetric experts.

There were some aspects of the study that proved problematic. The first related to the sizable proportion of cohort members who were deceased: about 60% of cases and 7% of controls. For these subjects, it was necessary to use proxy respondents to obtain data on exposure and confounding or modifying variables, with attendant uncertainties. Even with data from direct respondents, there is as yet no gold standard for judging the accuracy of radiation dose estimation. This is especially true with case-control designs in which there is potential for biased recall of events. Especially in light of the different proportion of proxy respondents in cases and controls, the influence of the source of information—direct or proxy—has been thoroughly evaluated in the analyses presented in paper III (*10*).

Although 87 cases of leukemia were confirmed by the expert Panel, for various reasons, including ineligibility, loss to follow-up and refusals, we were able to reconstruct radiation doses for only 71. These cases and their corresponding eligible controls comprise the sample for analysis (a total of 572).

Another challenge that faces all similar retrospective studies relates to the availability of bone marrow tissue for cases, which was particularly difficult in the earlier years of the study. Medical records were available for 100% of cases, and supporting biological material was present in almost 70% of cases sent for review. Indeed, the diagnostic confirmation of cases in this phase of the study was very good, and in an earlier feasibility study using an International Hematology Panel (*22*), it was shown that over 90% of the cases previously diagnosed with leukemia by Ukrainian hematologists could be confirmed if the medical record contained a report of a bone marrow study consistent with the diagnosis. Reliable clinical records documenting signs and symptoms of disease, clinical course, types of therapy and hematological responses increased the probability of accurate diagnosis. Although we were forced to use admission diagnoses for hospital case-finding because of the lack of discharge diagnostic data and may have lost a few acute leukemias as a result, we believe that due to the broad range of searches case ascertainment was quite complete.

Based on the studies reported to date, it has not been clear whether there is an increased risk of leukemia among Chornobyl cleanup workers. The current study, with its strong design and methods, contributes importantly to the weight of evidence. Our initial results, showing the dose–response analysis of radiation and leukemia, are reported in a companion paper (*10*).

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3. ПОШУК, ІДЕНТИФІКАЦІЯ ТА ВЕРИФІКАЦІЯ ДІАГНОСТИЧНИХ ДАНИХ ПРО ЗАХВОРЮВАННЯ

Для ідентифікації випадків лейкемії та РЩЗ використовувались альтернативні джерела персоналізованої інформації про потенційні випадки захворювань в когорті, а саме: бази даних ДРУ, Національного канцер-реєстру України (НКРУ), реєстр лейкемії, створений за даними регіональних і національних медичних установ. Інформаційні масиви баз даних спеціально розробленим програмним способом шляхом детерміністичного (з елементами імовірнісного) лінкіджу даних зв'зувались із файлом досліджуваної когорти ліквідаторів. Таким чином визначались індивідуальні записи ліквідаторів, наявні в обох масивах, тобто хворі члени когорти («випадки»).

Випадки раку щитоподібної залози було ідентифіковано **(підрозділ 3.1)** шляхом лінкіджу файлу когорти із базою даних НКРУ. Лінкідж включав функції порівняння повних імен, дати народження, а також адреси. Імовірнісні елементи процедури лінкіджу були адаптовані до національних особливостей правопису індивідуальних даних (імен), а також відсутніх відомостей (дат) в існуючих інформаційних масивах (реєстрах). Результати співпадіння записів підлягали експертизі і, за необхідності, уточненню із залученням додаткових даних. Процедура і програмне забезпечення лінкіджу даних були також використані для іТаким чином було ідентифіковано 196 випадків раку щитоподібної залози, які слугували основою для попереднього аналізу захворюваності на РЩЗ в досліджуваній когорті, а пізніше – для оцінки ризиків. Розрахований стандартизований за віком показник захворюваності на РЩЗ в досдіджуваній когорті (SIR) впродовж 1986-2010 склав 3,50 (95% довірчий інтервал [CI]: 3,04–4,03) із найбільшими значеннями для періоду 1995–2005 рр. Щодо верифікації діагнозів випадків раку щитоподібної залози, враховувався рівень

гістологічного підтвердження цих захворювань (97,5 %), заявлений в офіційно опублікованих бюлетенях Національного канцер-реєстру України

Підрозділ 3.2 присвячений процедурі верифікації діагнозів лейкемії і споріднених захворювань, основною ланкою якої є двоетапна (локальна і незалежна міжнародна) діагностична експертиза. Процедуру проведення незалежної діагностичної гематологічної експертизи випадків лейкемії було розроблено і попередньо протестовано на обмеженій вибірці (n=62) випадково відібраних випадків лейкемії, мієлодиспластичного синдрому та множинної мієломи з числа діагностованих у загальній популяції чоловічої статі 1926–1972 рр. народження.

Метою такої експертизи було відпрацювати етапи підготовки і проведення експертизи, вивчити можливості забезпечення діагностичним матеріалом (клінічними записами, препаратами периферійної крові та червоного кісткового мозку). Крім того, метою було оцінити якість діагностичних матеріалів, наявних в українських медичних установах, і можливість узгодження використаних діагностичних класифікацій з міжнародними. Було розроблено спеціальну коротку клінічну форму, в яку вносились клініко-лабораторні дані, і яка підлягала діагностичній експертизі разом із спеціально закодованими взірцями діагностичних препаратів. Були розроблені паперові і електронні форми для фіксації індивідуальних і консенсусних рішень експертної комісії. Робоче місце кожного експерта було забезпечено мікроскопом із високими оптичними характеристиками. Спочатку роботи було узгоджено критерії і класифікації для використання під час експертизи.

За результатами експертизи було визначено задовільну якість та доступність діагностичних матеріалів. В цілому, було підтверджено діагнози в 49 (79%) із 62 випадків, представлених на перегляд. В тому числі було підтверджено 34 (89 %) із 38 випадків лейкемії. 4 основні сесії експертизи в подальшому проходили за методологією у точній відповідності із попередньо протестованою.

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Thyroid cancer incidence in Chornobyl liquidators in Ukraine: SIR analysis, 1986–2010

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Abstract We studied thyroid cancer incidence in a cohort of 150,813 male Chornobyl clean-up workers ("liquidators") from Ukraine by calculating standardized incidence ratio (SIR) using national cancer statistics. Follow-up began on the liquidator's registration date with the Chornobyl State Registry of Ukraine (the earliest date was 05. 05. 1986) and continued through December 31, 2010, date of thyroid cancer diagnosis, date of death, or date of last known vital status, whichever came first. There were 196 incident thyroid cancers in the study cohort with an overall SIR of 3.50 [95 % confidence interval (CI) 3.04–4.03]. A significantly elevated SIR estimate of 3.86 (95 % CI 3.26–4.57) was observed for liquidators who had their first clean-up mission in the Chornobyl zone in 1986, when levels of external and internal exposure to radiation were highest; the SIR estimates for later calendar years of first clean-up mission, while significantly elevated, were lower. The SIR estimates were elevated throughout the entire follow-up period but were especially high 10–18 years after the accident: 4.62 (95 % CI 3.47–6.15) and 4.80 (95 % CI 3.78–6.10) for the period 1995–1999 and 2000–2004, respectively. Our findings support the growing evidence of increased thyroid cancer rates among Chornobyl liquidators. Although this could be partially attributed to increased medical surveillance, the observed pattern of SIR increase warrants further investigation of a potential contribution of radiation exposure to the elevated thyroid cancer rates in this large population.

Keywords Thyroid cancer · Liquidators · Clean-up workers · Chornobyl · Chernobyl · Ukraine

Abbreviations

AHS	Adult health study
CI	Confidence interval
ERR	Excess relative risk
Gy	Gray
PYR	Person-year
PIR	Proportional incidence ratio
SIR	Standardized incidence ratio
CSRU	Chornobyl State Registry of Ukraine
UNCR	Ukrainian National Cancer Registry

Introduction

After the accident at the Chornobyl (Chernobyl) nuclear power plant on April 26, 1986, over 500,000 individuals, predominantly males, were involved in radiation emergency response, containment and clean-up activities through 1990 [1]. The clean-up workers (also known as "liquidators") received external exposure to numerous radioactive materials deposited on the ground and building surfaces. The highest levels of exposure to various organs in the body, including the thyroid, occurred during 1986–1987 [1]. In addition, individuals who were involved

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in recovery work during the first weeks after the accident may have received considerable thyroid doses due to internal exposure to radioactive iodine (^{131}I). Early studies based on standardized incidence ratio (SIR) analyses suggested an excess of thyroid cancers in liquidators from various countries, including the Russian Federation, Ukraine, Estonia and Latvia, as compared with the general population [2–4]. More recently, a significantly increased risk of thyroid cancer associated with total and ^{131}I thyroid doses was reported in a case–control study of liquidators from Belarus, Russian Federation and Baltic countries [5].

The Ukrainian liquidators comprise nearly half of all Chornobyl recovery workers officially registered during the period of 1986–1991 [1], and include those who were involved in the most difficult early operations at the Chornobyl site and within the 30-km zone. Ukrainian liquidators have the highest mean external doses of all liquidators from the countries involved [1]. Here we present results from the SIR analysis of thyroid cancer incidence in a large cohort of Ukrainian male liquidators (n = 150,813) over the 1986–2010 period, up to almost 25 years after the Chornobyl accident. Thyroid cancer rates in the cohort were compared with national rates in males, focusing on calendar time and age trends in thyroid cancer risk.

Materials and methods

The study cohort of 150,813 male liquidators was defined based on data from the Chornobyl State Registry of Ukraine (CSRU), an official register established in 1986 to monitor the health status of several population groups, including recovery and clean-up workers, exposed to radiation due to the accident [1, 6]. The study cohort includes liquidators resided in six oblasts (Kyiv, Donetsk, Dnipropetrivsk, Kharkiv, Cherkassy, and Chernihiv) and Kyiv city that is about 60 % of all liquidators registered in the CSRU. Those areas have high quality of oncology service and cancer register operation, as well as preservation of morphological materials. Information on vital status and current address of individuals registered with the CSRU is annually updated through reporting from medical institutions performing liquidator's follow-up. About 80 % of liquidators undergo annual medical examination. In case of contradictory or incomplete information, for example on death cases, additional tracing is performed through policlinics, vital statistics bureau, and address bureau. We performed our analysis using the update performed in 2011. Incident thyroid cancer cases were ascertained by linkage of the study cohort with the Ukrainian National Cancer Registry (UNCR). The UNCR is a population-based computerized cancer registry which reached nearly nationwide coverage in 1997 [6]. All incident cancer cases diagnosed before 1997 and survived until 1997 were retrospectively included in the UNCR. The majority of diagnoses reported to the UNCR come from specialized oncology hospitals, and 97.5 % of thyroid cancer diagnoses are histologically verified (http://users.i.kiev.ua/~ucr/). The linkage procedure was based on a computerized deterministic record linkage technique with probabilistic elements incorporating a set of comparison functions using full name, date of birth, and complete residential address [7]. Each computer link also was considered by the team of Ukrainian researchers to confirm its identity. Only thyroid cancer cases with confirmed identity were included in the study.

The follow-up began on the date of an individual's registration with the CSRU and ended on the date of thyroid cancer diagnosis, date of death, date of last known vital status, or December 31, 2010 (end of follow-up), whichever came first. When only the year of thyroid cancer diagnosis or death was available, we assigned July 2 as the month and day of cancer diagnosis or death. Person-years (PYRs) at risk and incident thyroid cancer cases were tabulated over oblast (or province) of residence, year of first clean-up mission in the Chornobyl zone (1986/1987/1988+/ unknown), attained age in 5-year categories from 18 through 82 years (<20/25/30/35/40/45/50/55/60/65/70/75/80+), calendar period (1986/1990/1995/2000/2005–2010), and age at first clean-up mission in 5-year categories from 18 through 60 years (<20/25/30/35/40/45/50/55+). Calculation of PYRs and ratios of observed to expect number of thyroid cancer cases [standardized incidence ratios (SIRs)] were performed using Epicure software [8]. We estimated the number of expected incident thyroid cancer cases by applying calendar-time and age-specific thyroid cancer incidence rates for the entire male population of Ukraine (http://users.iptelecom.net.ua/~ucr/download/download.htm) to the respective cohort-specific PYRs. The SIRs and their 95 % confidence intervals (CI) were calculated assuming Poisson distribution of grouped incidence data with significance tests and CIs determined directly from maximum likelihood analyses. All p-values refer to two-sided tests with a p value of <0.05 considered statistically significant.

Results

Selected characteristics of the study cohort are presented in Table 1. At the time of registration with the CSRU, 43 % of the cohort resided in Kyiv city or Kyiv oblast; a higher proportion of liquidators with thyroid cancer were Kyiv city residents compared with those free of thyroid cancer (38 and 26 %, respectively). At the end of follow-up, mean age of liquidators with or without thyroid cancer was about

Table 1 Main characteristics of the Ukrainian liquidators' cohort

Characteristics	Thyroid cancer (n = 196)	Thyroid cancer-free subjects (n = 150,617)
Oblast of residency		
Kyiv city	74 (37.8 %)	38,974 (25.9 %)
Kyiv	34 (17.3 %)	25,724 (17.1 %)
Donetsk	24 (12.2 %)	22,164 (14.7 %)
Dnipropetrivsk	26 (13.3 %)	20,165 (13.4 %)
Kharkiv	14 (7.1 %)	17,579 (11.7 %)
Chernihiv	14 (7.1 %)	13,310 (8.8 %)
Cherkassy	10 (5.1 %)	12,701 (8.4 %)
Mean attained age, years (±SD)	51.5 ± 10.5	51.8 ± 9.6
Percentage of liquidators with first mission in 1986	68.9	62.2
Percentage of liquidators with unknown year of first mission	9.2	7.4

Vital status as of 31. 12. 2010	Subjects	%
Alive	107,835	71.5
Deceased	17,483	11.6
Emigrated or lost to follow-up	25,495	16.9

Table 2 Thyroid cancers, person-years and SIRs in the cohort of Ukrainian liquidators by follow-up period

Follow-up period	Number of liquidators under follow-up	Person-years	Mean age at exposure, years	Thyroid cancer cases		SIR[a], 95 % CI
				Observed	Expected	
1986–89	55,175	104,925	32.7	3	1.1	2.61 0.84–8.09
1990–94	91,512	347,043	33.2	13	7.0	1.84 1.07–3.18
1995–99	114,663	450,537	33.7	47	10.2	4.62 3.47–6.15
2000–04	123,638	515,192	33.8	67	14.0	4.80 3.78–6.10
2005–10	107,982	565,799	33.4	66	23.7	2.79 2.20–3.55
Total	150,813	1,983,496	33.5	196	56.0	3.50 3.04–4.03

[a] Model adjusted for attained age and oblast of residence

52 years; 12 % of the cohort members were deceased and 17 % were emigrated or lost to follow-up. Among liquidators with thyroid cancer, 69 % had their first mission in the Chornobyl zone in 1986 compared with 62 % of liquidators without thyroid cancer.

During the entire follow-up period through December 31, 2010, 196 incident thyroid cancer cases were observed in the cohort. This number was significantly higher than the expected number of 56, providing an elevated SIR estimate of 3.50 (95 % CI 3.04–4.03). Although crude thyroid cancer incidence rates increased with increasing attained age (data not shown), SIRs did not differ significantly by age (SIR = 5.06 for attained age <30 years; SIR = 3.61 for 30–39 years; SIR = 3.56 for 40–49 years; SIR = 2.78 for 50–59 years; SIR = 4.72 for 60+ years, p for heterogeneity = 0.12).

Table 3 Thyroid cancers, person-years and SIRs in the cohort of Ukrainian liquidators by year of first mission in the Chornobyl zone

Year of first mission	Mean age at exposure, years	Mean attained age at the end of follow-up, years	Person-years	Thyroid cancer cases		SIR[a], 95 % CI
				Observed	Expected	
1986	33.5	52.6	1,233,836	135	35.0	3.86 3.26–4.57
1987	32.4	49.4	365,599	28	9.6	2.91 2.01–4.21
1988+	35.0	49.9	288,844	15	8.1	1.84 1.11–3.06
Unknown	Unknown	54.0	95,217	18	3.3	5.48 3.45–8.69
Total	33.5	51.8	1,983,496	196	56.0	3.50 3.04–4.03

[a] Model adjusted for attained age, oblast of residence and calendar period

The SIRs were elevated throughout the follow-up period (Table 2), ranging between 1.84 and 4.80, and were statistically significant, except for the earliest follow-up period of 1986–1989 (p for heterogeneity <0.001). SIR estimates were highest at 10–18 years after the accident, i.e., during the periods 1995–1999 and 2000–2004 (SIR = 4.62 and 4.80, respectively). In later years (2005–2010), the SIR decreased to 2.79 but remained statistically significant ($p < 0.001$).

Table 3 shows SIRs by calendar year of first mission in the Chornobyl zone (p for heterogeneity = 0.004). Among study participants with known year of first mission (93 %), about two-thirds began their recovery work in 1986 and had the highest SIR estimate of 3.86 (95 % CI 3.26–4.57). Lower but significantly elevated SIRs were observed for liquidators who had their first mission in 1987 and in 1988 or later (SIR = 2.91, 95 % CI 2.01–4.21 and 1.84, 95 % CI 1.11–3.06, respectively). Liquidators with unknown year of first mission had a high SIR estimate of 5.48 (95 % CI 3.45–8.69). Among those with known year of first mission, there was no variation in SIR by age at first mission (mean = 33.5 years) or attained age (data not shown, p for heterogeneity = 0.86 for age at first mission and 0.24 for attained age, respectively).

Discussion

We found the highest, almost fourfold increase in thyroid cancer incidence among the liquidators who had the first clean-up mission in 1986. Based on crudely estimated external doses determined from officially recorded information and through other methods, the early 1986 liquidators, as a group, had a higher level of exposure than those who participated in the recovery and clean-up activities in 1987 or later [1]. This group also includes individuals who potentially had exposure to ^{131}I, which remained elevated from April to June after the accident. Our data showed that the SIRs decreased but remained elevated among those who started their clean-up activities in 1987 or later. Another important finding relates to the time trend of SIRs, which reached their highest level about 10–18 years after the accident. The SIR for later calendar years was lower but statistically significant.

We consider our study to have improvements in several aspects over the one published previously [3]. The present results are based on a larger cohort (n = 150,813) of Ukrainian male liquidators including liquidators with both early (1986–1987) and late (1988+) years of first mission. The follow-up of the cohort was extended through 2010, and the study area was expanded to include two additional oblasts. Unlike the previous study, in which thyroid cancer cases were identified from the CSRU and may have included cases without histological verification, all thyroid cancers in our study were identified through the linkage with the UNCR including cases diagnosed before 1997, the year when UNCR reached nearly nationwide coverage. Since survival rates are high for most common types of thyroid cancer (papillary and follicular carcinomas), thyroid cancer data in the UNCR are considered to be nearly complete, especially for papillary carcinoma—the type known to be radiosensitive [9].

The overall SIR estimate of 3.5 observed in our study is similar in magnitude to that reported by Ivanov et al. [2] for Russian liquidators followed from 1986 to 2003 (SIR = 3.47, 95 % CI 2.80–4.25). Ivanov et al. also found the highest SIR of 6.62 among early liquidators (April–July 1986) and lower SIRs of 2.00–3.44 among liquidators first employed in August 1986–1990 [2]. A significantly increased thyroid cancer incidence rate has also been found in liquidators from Baltic countries [proportional incidence ratio (PIR) = 2.76, 95 % CI 1.63–4.36], again with the

highest estimate found among liquidators of May–April 1986 (PIR = 6.38, 95 % CI 2.34–13.89) [10]. In our study, only 56.7 % of liquidators (85,486 of 150,813) had information about month and year of first clean-up mission. Among them, the highest SIR of 4.19 (95 % CI 3.02–5.81) was found in liquidators who had their first mission in April–June 1986 (data not shown), which is consistent with the pattern observed in early liquidators from Russian Federation and Baltic countries [2, 10].

The present data, as with most SIR studies, have limitations. The most important ones relate to a possible detection bias for thyroid cancer due to a screening effect, which is well known for thyroid cancer, and lack of individual thyroid dose estimates. We could not address the screening question directly, but we note that all liquidators in Ukraine are entitled to similar medical care benefits regardless of when they participated in clean-up activities or what activities they performed in the zone. Therefore, the SIR pattern by year of first clean-up mission or calendar time would appear unlikely to be explained by a differential screening effect among the various subgroups of liquidators. It is also important to recognize that the medical care provided to liquidators does not routinely involve thyroid screening examinations, such as ultra-sonogram, palpation, etc., that can identify asymptomatic thyroid tumors, which are not detected otherwise. However, closer medical attention may increase a chance of diagnosing cancer, but this effect is difficult to quantify precisely. Based on comparison of thyroid cancer baseline rates between Adult Health Study (AHS) subjects and non-AHS subjects in the atomic bomb survivors, the screening effect has been estimated to be around 2.5 [11]. The SIR of 3.86 for the 1986 liquidators (Table 3) as well as calendar-time-specific estimates of 4.62 and 4.80 for the periods of 1995–1999 and 2000–2004, respectively, (Table 2) exceed 2.5, and one may suppose that these excess SIRs may be in part attributed to radiation exposure. We were concerned that some of the liquidators, especially those registered with CSRU many years after the accident, could have registered for health reasons (e.g., cancer) and thus may have spuriously led to increased cancer rates. To address this concern, we repeated the analysis starting follow-up one year later after the SCRU registration and, therefore, excluding cases diagnosed within one year of registration. The SIRs were not substantially affected and remained significant (SIR = 3.78 for 1995–1999; 4.37 for 2000–2004; and 2.81 for 2005–2010). It appears that registration related to health reasons had a minimal, if any, effect on the SIRs in these calendar years. Another study limitation is that our results are based on a Poisson regression model which is not effective in reducing potential overdispersion in data. As a result, a standard error for model parameters could be underestimated, leading to narrowing of true confidence intervals [12].

A high risk of thyroid cancer following radiation exposure during childhood and adolescence is widely known and well documented [11, 13–15]. The SIR findings from the present and other studies suggest a substantial increase in thyroid cancer rates among Chornobyl liquidators exposed to radiation during adulthood [2–4, 10]. Because of the limitations associated with ecological studies [16], one should be cautious in drawing conclusion about the radiation effect or quantifying estimates of radiation risk using SIR data. Therefore, it is especially noteworthy that a recent case–control study among liquidators from Belarus, Russian Federation and Baltic countries demonstrated a significant dose response for thyroid cancer, with an estimated excess relative risk per 100 mGy (ERR/100 mGy) in male liquidators of 2.9 for total thyroid dose [5]. The high ERR/Gy reported in [5] is comparable to risk estimates for subjects exposed under 20 years of age [17], and this is contrary to the view that the risk of thyroid cancer from adult radiation exposure is low. However, epidemiological data on the risk of thyroid cancer following adult exposure are still limited and there is diversity in estimates of the radiation-related risk of thyroid cancer reported in the literature [18–21].

Among the liquidators of the case–control study [5], ^{131}I doses comprised about 85 % of the total thyroid dose, mostly due to consumption of ^{131}I-contaminated food while the liquidators were at their home residence. The Ukrainian liquidators who resided in contaminated areas during the first two months after the accident may have had significant exposure to ^{131}I from dietary sources as well. However, information on residential history was available from the SCRU only at the time of registration, but not during the two months after the accident.

The high SIR for liquidators with unknown year of first mission has an important implication, as this group may include a substantial number of early liquidators exposed to higher levels of radiation. We note that a majority (87 %) of the liquidators with unknown year of first mission were residents of Kyiv oblast or city. The liquidators recruited immediately after the accident, were mostly from Kyiv oblast or city. In the study cohort, 54 % of the liquidators with first clean-up mission in 1986 resided in Kyiv oblast or city. For those who were recruited in 1987 or later, the proportion of residents from Kyiv oblast or city was only 8.7 %.

In summary, we believe that our findings, together with findings by others, provide evidence of increased rates of thyroid cancer among Ukrainian liquidators. Although this could be partially attributed to increased medical surveillance, the increased risk of thyroid cancer among those who participated in recovery operations soon after the accident and the high risk appearing 10–20 years after the accident suggest the potential for radiation effect. In liquidators there are complex exposure situations involving

both external and internal irradiation that varied by type of clean-up activities, time, and location. These cannot be adequately investigated by ecological studies. A well-designed epidemiological study with individually reconstructed thyroid doses is warranted to investigate a potential contribution of radiation exposure to the excess of thyroid cancer among Ukrainian liquidators.

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Conflict of interest The authors declare that they have no conflict of interest.

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Histologic Verification of Leukemia, Myelodysplasia, and Multiple Myeloma Diagnoses in Patients in Ukraine, 1987-1998

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Abstract

In preparation for a possible large epidemiological study of radiation-related leukemia in Chernobyl clean-up workers of Ukraine, histologic evaluation of 62 cases of leukemia and related disorders was conducted by a panel of expert hematologists and hematopathologists from the United States, France, and Ukraine. All cases were randomly selected from a surrogate population of men in the general population of 6 regions of Ukraine who were between the ages of 20 and 60 years in 1986 and were reported to have developed leukemia, myelodysplasia, or multiple myeloma between the years 1987 and 1998. The hematologists and hematopathologists on the panel were in agreement with one another and with the previously reported diagnoses and classifications of about 90% of the cases of acute and chronic leukemia in the study. These results suggest that strong reliance can be placed on the clinical diagnoses of acute and chronic forms of leukemia and multiple myeloma that have occurred in Ukrainian Chernobyl clean-up workers providing that the diagnoses are supported by records of the patients having had adequate histologic bone marrow studies. The number of cases in this study with the diagnosis of myelodysplasia, however, was too small to draw firm conclusions. *Int J Hematol.* 2002;76:55-60.

Key words: Ukraine; Leukemia; Multiple myeloma; Myelodysplasia

1. Introduction

The primary objective of the study in this report was to determine the extent to which the diagnosis and classification of leukemia in Chernobyl accident clean-up workers of Ukraine who were reported to have developed leukemia following the accident might be histologically verified by Western standards. This hematology review was an important part of a 2-year study initiated in November 1997 by the National Cancer Institute in the United States and the Research Center for Radiation Medicine (RCRM) in Ukraine to determine the feasibility of conducting a large retrospective radiation dose–related study primarily of cases of leukemia, but also of myelodysplasia (MDS) and

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multiple myeloma (MM) in Chernobyl accident clean-up workers of Ukraine, occurring between 1987 and 1998 [1]. The study consisted of a review by a highly qualified group of hematologists and hematopathologists from Ukraine and 2 Western countries of bone marrow slides and abstracted medical records from cases of randomly selected adult men in the general populations of 5 specific regions of Ukraine who were reported to have developed leukemia, MDS, or MM between the years 1987 and 1998. These men were selected for the histologic review to serve as surrogates for the Chernobyl accident clean-up workers with leukemia or one of the other disorders.

Currently there is considerable interest in demonstrating the possibility of increased leukemia in the radiation-exposed clean-up workers of the Chernobyl accident. The Chernobyl clean-up workers comprise a large population of men with radiation exposures in considerable excess of those received by the general population from fallout. Much of the interest in this group of workers is because of the uncertain influence on the extent of leukemia induction of their relatively slow rate of radiation exposure compared to the almost instantaneous exposure of the atomic bomb survivors for whom there now are well-established dose-response relationships [2]. This difference is of considerable importance in the projection of possible similar effects, not only to the general population exposed to the fallout of the Chernobyl accident, but also to nuclear power and other radiation workers throughout the world whose rates of radiation exposure are much more similar to those of the Chernobyl clean-up workers than to those of the atomic bomb survivors. It also is expected that the extent of the radiation induction of leukemia in the clean-up workers will provide a good index of the extent of any possible excess cancer burden among others exposed to radiation from the Chernobyl accident.

Several recent reports based on information derived from registries and other sources suggest that the incidence of leukemia may be increased in Chernobyl accident clean-up workers, especially for those who worked during the years 1986 and 1987 [3-8]. The results of 1 of these reports [4] have been reported to be flawed primarily on the basis of the use of an inappropriate comparison population and inclusion of cases of chronic lymphocytic leukemia (CLL), a type of leukemia that has never been demonstrated to be increased in any human radiation-exposed population [9,10]. A subsequent published report based on the same cohort of liquidators with the exclusion of CLL cases and with other modifications in methodology showed no significant correlation between leukemia risk and radiation exposure or evidence of a dose-related trend [5]. The completeness of case ascertainment in the other studies of leukemia in the Chernobyl clean-up workers is uncertain, and there is little evidence that the cases included in those reports were subjected to rigid and impartial histologic review for verification of diagnosis. A number of excellent studies relating ionizing radiation exposure to the occurrence of leukemia have recognized that histologic verification of diagnosis is an essential component of the study [11-18]. The leukemia reports of the Chernobyl clean-up workers also raise questions of whether the diagnosis and classification of leukemia cases in those reports meet the currently accepted international diagnostic criteria and terminology standards that are used by hematologists in the United States and western Europe.

The present review provides valuable information about whether the diagnosis and classification of cases of leukemia and also of MDS and MM that occurred in the adult male population of Ukraine during the 10 years following the Chernobyl accident can be histologically verified in accordance with internationally accepted hematology standards. The study also provides considerable information regarding the quality of stored bone marrow slides in Ukrainian hospitals. The results of this study are very useful in the consideration of conducting future histologically verified studies of the possible retrospective radiation induction of leukemia and some related disorders in the Ukrainian Chernobyl accident clean-up workers.

2. Materials and Methods

Data recording forms were developed, and the hematology panel members were provided with a considerable amount of background information concerning the objectives of the review. During the several months prior to the hematology panel session in Kiev, in which the bone marrow slides and abstracted clinical records of the cases were reviewed, 6 regions of Ukraine were tentatively identified as suitable for a future detailed study of leukemia in the Chernobyl clean-up workers within their resident populations. With 1 exception, each of the regions selected was an oblast (roughly equivalent to a state in the United States). The exception was Kiev City, the largest metropolitan area in Ukraine.

The objectives and research plans for the hematology pilot project were described to hospital officials and physicians by one or more senior hematologists from RCRM to obtain their permission to abstract records and to borrow bone marrow slides for review by members of an international panel of expert hematologists. A small team from the RCRM in Kiev, including an epidemiologist and a hematologist, then visited appropriate hospitals and clinics in the 6 target areas to collect materials for the review.

Men aged 20 to 60 years, in the general population, who were reported to have developed leukemia, MDS, or MM between the years 1987 and 1998 in any of the 6 regions of Ukraine in the proposed study for each of 3 time periods (1987-1990, 1991-1994, and 1995-1998), were randomly selected from hospital or clinic lists of patients for whom a pretreatment bone marrow aspiration smear was known to be available. The number of cases of each type of disease requested for evaluation from each region is shown in Table 1. Whenever 2 cases of a particular type of disease were required, 1 case was selected from the early period and the other from the most recent period. Similarly, if 5 cases were required, 2 were chosen from the earliest period, 1 from the middle period, and 2 from the latest period. The purpose of this selection process was to make certain that bone marrow slides from persons who had developed one of the diseases of interest during both the early and more recent years following the Chernobyl accident were examined.

Table 1.
Cases of Hematologic Disorders Requested from 6 Regions in Ukraine for Histologic Verification (Men, Aged 20-60 Years), 1987-1998

Diagnosis	No. of Cases Requested from Each Region	Total No. of Cases Requested from All 6 Regions
Chronic myelogenous leukemia	2	12
Chronic lymphocytic leukemia	2	12
Acute leukemia (any type)	5	30
Myelodysplasia	2	12
Multiple myeloma	2	12
Total	13	78

The histologic review sessions were conducted at the RCRM by the members of the expert review panel in Kiev over a period of 4 working days. At the outset it was stressed that the major objective of the review was to determine whether the expert panel members could confirm with reasonable certainty the clinical diagnosis of leukemia for each case. Other important objectives of the review were to evaluate differences in the classification of types of leukemia that might exist between the hematologists of Ukraine and those of the Western countries, the extent to which the diagnosis of MDS and MM could be confirmed, and the quality of the bone marrow slides and abstracted clinical records. The panelists agreed at the outset of the review that the criteria for the diagnoses of acute leukemia and MDS would be in accordance with the French-American-British (FAB) system with the minimum requirement of 30% blasts in the bone marrow smear for the histologic diagnosis of acute leukemia [19,20]. The minimum number of typical plasma cells in the bone marrow smear required for the histologic diagnosis of MM was 10% [21].

Following agreement on procedures to be used, the panelists reviewed 5 cases at a time and recorded their impressions on their worksheets regarding disease diagnosis, disease classification, and the quality of histologic materials and clinical records. One member of the panel then chaired open discussions of 10 cases at a time to achieve a consensus regarding disease diagnosis and classification. The process was continued in this fashion with daily rotation of discussion chairpersons until conclusions were reached for all cases in the study. All histologic materials were carefully returned to their hospitals of origin upon completion of the slide reviews.

3. Results

Bone marrow aspiration smears from 45 cases of leukemia, 6 cases of MDS, and 11 cases of MM were identified by a random selection process (Table 2). Selection of cases from the entire adult male general populations of the 6 target areas in Ukraine resulted in the identification, using bone marrow slides, of only 62 cases of the various types of leukemia and related disorders rather than the 78 cases proposed for evaluation in accordance with the randomized selection process (Tables 1 and 2). The study was 16 cases short of the objective number, principally because of failure to identify enough cases of myelodysplasia during the early period of 1987-1990 and the almost complete absence of cases in one region where a natural disaster has destroyed most of their archived hematology slides.

The diagnosis of leukemia was histologically confirmed by members of the panel for 38 (84%) of the previously diagnosed cases of leukemia (Table 2). Exclusion of the 1 case of chronic lymphocytic leukemia (CLL) and 2 cases of chronic myelogenous leukemia (CML), for which only poor quality slides that were inadequate for diagnosis were available, improved the confirmation rate to 90%. It also should be noted that 3 of the 4 remaining cases that were not confirmed as leukemia were reclassified as MDS. All 3 cases previously had been classified as acute myelogenous leukemia (AML). Eight of the 11 cases of MM, for which bone marrow slides were available, were confirmed by members of the panel (Table 2) by consensus. On the other hand, panel members confirmed only 3 of the 6 cases of MDS (Table 2). The low confirmation rate for the 6 cases of MDS was the result of the reclassification of 3 of these cases as AML. Concurrence rates with the consensus diagnosis of leukemia for the 2 Ukrainian panel members and the 3 panel members from the United States and France were 92% and 85%, respectively.

Panel members classified all cases of acute leukemia by FAB but, because none of the previous Ukrainian cases had been classified by FAB, comparisons for all types of leukemia

Table 2.
Histologic Confirmation of the Diagnoses of Leukemia, Myelodysplasia, and Multiple Myeloma for Ukrainian Men, Aged 20-60 Years, by International Panel Members, 1987-1998

Reported Diagnosis	No. of Cases	Total No. of Cases Confirmed	% of Total Confirmed	No. of Cases with Inadequate Histology*	% of Cases Confirmed with Adequate Histology
Acute leukemia	28	24†	86	0	86
Chronic myelogenous leukemia	9	7	78	2	100
Chronic lymphocytic leukemia	8	7	88	1	100
Myelodysplasia	6	3‡	50	0	50
Multiple myeloma	11	8	73	2	89
All disorders combined	62	49	79	5	86

*Number of cases with bone marrow slides of such poor quality that they were undiagnosable.
†Three of the 4 cases not confirmed as acute leukemia were reclassified as myelodysplasia.
‡All 3 cases not confirmed as myelodysplasia were reclassified as acute leukemia.

Table 3.
Histologic Confirmation of the Type of Leukemia by Members of an International Hematology Panel Compared to Previous Classifications by Regional Hematologists in Ukraine

Reported Type of Leukemia	No. of Cases	No. Verified for Type of Leukemia	% Verified for Type of Leukemia
Acute myelogenous	10	9*	90
Acute lymphocytic	5	4†	80
Acute, other types	9	7‡	78
Chronic myelogenous	7	7	100
Chronic lymphocytic	7	7	100
All types combined	38	34	89

*One case was reclassified as acute lymphocytic leukemia.
†One case was reclassified as acute leukemia, type uncertain.
‡Two cases were reclassified as acute myelogenous leukemia.

were made in accordance with standard International Classification of Diseases terminology. The type of leukemia previously diagnosed was verified by members of the panel for 34 (89%) of the 38 proven cases of leukemia (Table 3). All 7 of the cases diagnosed as either CML or CLL were confirmed by members of the panel (Table 3). Panel members agreed with the diagnosis of leukemia type for 20 (83%) of the 24 cases of acute leukemia. This group of cases included 9 of 10 cases of AML and 4 of the 5 cases of acute lymphocytic leukemia (ALL). Two previously unclassified cases of acute leukemia were reclassified as AML. The rate of agreement with the type of acute leukemia as determined by consensus for the Ukrainian members of the panel was 85% compared to 80% for the panel members from the United States and France. Agreement by both groups for determination of the types of chronic leukemia was more than 90%.

Bone marrow aspiration smear quality generally was quite good. In only 3 of the 45 cases, because of poor smear quality, it was not possible to establish the diagnosis of leukemia. However, only about half of the smears examined were considered to be of excellent quality, because of such factors as faded stain, excessive dilution of marrow cells, or coverslip artifact. Bone marrow smear quality had little relationship to the time of disease occurrence. Abstracted information from medical records was generally very complete and almost invariably contained important information in support of the diagnosis of the underlying hematologic disorder.

4. Discussion

The results of this study strongly suggest that for at least the past 10 years there have been close similarities regarding the histologic diagnosis and classification of the major types of leukemia among the hematologists in Ukraine, western Europe, and the United States. These findings therefore suggest that clinical records that verify completion of an adequate pretherapy bone marrow aspiration smear almost invariably reflect an accurate diagnosis and classification for the major types of leukemia. This information is of particular importance for the proposed retrospective Chernobyl clean-up worker leukemia study because, during the immediate post-Chernobyl years, patients' bone marrow slides not infrequently were lost or destroyed, whereas their clinical records were more often retained and maintained in a good state of preservation.

There were several reasons for initially conducting the study on adult male members of the general population rather than on the clean-up workers. The logistical problems associated with a wide geographic search in Ukraine for an adequate number of the different types of leukemia in the clean-up worker population appeared quite formidable. The selection of a cohort of Chernobyl clean-up workers for the proposed epidemiological study of leukemia was still incomplete at the time of the review, and its completion appeared to be many months ahead. It also seemed unlikely that the proposed Chernobyl clean-up worker cohort was large enough to provide enough cases of the various types of leukemia to satisfy the requirements for expert hematology panel review.

Evidence that MDS is a radiation-induced disorder is scanty but certainly is sufficient to recommend that this disease be included in any study of radiation-induced leukemia [12,22-28]. One problem with the inclusion of MDS in such studies is that the clinical presentation and morphologic characteristics of MDS and AML frequently are so similar that diagnostic differentiation between advanced MDS and AML may be extremely difficult, particularly in the absence of cytogenetic and special histochemical studies [22]. Primary MDS is a clonal stem cell disorder with a rate of progression from its most advanced form, refractory anemia with excess blasts in transformation (RAEB-t), to acute nonlymphocytic leukemia reported to be in the range of 40% to 60% [29,30]. Actuarial studies of the transition rates of certain advanced primary forms of MDS to acute nonlymphocytic leukemia are reported to be 100%, implying that the border between RAEB-t and AML is completely arbitrary [31]. The relationship between secondary MDS and AML is so close that a recommendation also has been made that MDS should not be separately identified in any study of secondary leukemia [23]. The blurring of diagnostic criteria between either MDS associated with a large number of blast cells or some secondary forms of MDS and AML also has been emphasized in the recent World Health Organization recommendations for the classification of hematologic malignancies [32].

The earliest case recorded as MDS in this series was in 1993, but there is considerable evidence that the disorder was recognized by Western hematologists a number of years before that time. Perhaps general unfamiliarity with this disorder among Ukrainian hematologists 10 to 15 years ago, along with the problem of separating many cases of MDS from AML, difficult even for many expert hematologists, accounted for the reclassification to acute leukemia of 3 of the 6 cases of MDS included in the study. In a similar fashion, if 3 of the AML cases had not been reclassified as MDS, the confirmation rate for AML would have been more than 95% (Table 2).

The number of cases of MM included in this pilot study was too small to draw strong conclusions, but the results suggest that a more extensive study of this disorder in relation to radiation exposure is quite feasible. The case for radiation induction of MM remains somewhat controversial, but there are several reasons why a radiation dose-response study of MM in the clean-up workers could be important [2,33-39].

The age distribution of the male nuclear power workers for whom studies at some nuclear power sites have shown an increased risk of radiation-induced MM is quite similar [33,34,37,38]. Although the current number of person-years for a retrospective study of MM for the population of the approximately 100,000 Ukrainian clean-up workers proposed for a future study of leukemia is moderately less than that for the nuclear power workers in the 3-country study, the estimated cumulative radiation dose for the entire cohort of clean-up workers in the proposed study is several times greater than that for the nuclear power workers. This calculation is based on an average clean-up worker radiation dose estimate of approximately 110 mGy [40]. Finally, it should be mentioned that even if the current latent period for determination of radiation-induced risk for MM in the clean-up workers is too short, or if the population of workers is too young to provide conclusive results, a study at this time should provide the groundwork for future investigations.

Overall, the information derived from this study provides strong support for acceptance of the diagnoses of the chronic and acute leukemias that have occurred in Ukrainian Chernobyl clean-up workers following the accident, providing the diagnoses were supported by bone marrow examinations. This study also suggests that the previous histologic diagnosis of cases of MM in this population has been quite reliable. Too few cases of MDS were evaluated to draw any firm conclusions, but the results suggest that most cases reported with this disorder are either correctly diagnosed MDS or cases of AML. Such information is of considerable importance as a background for the future conduct of retrospective studies of radiation dose-response relationships for the occurrence of leukemia, myelodysplasia, and MM in Chernobyl clean-up workers of Ukraine. It is likely that bone marrow slides for many of the cases will not be located at this late date, but if the clinical information and bone marrow reports are consistent, the diagnoses of leukemia and MM should be accepted.

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4. ДОЗИМЕТРИЧНИЙ СУПРОВІД ДОСЛІДЖЕННЯ

Одним із визначальних елементів аналітичного дослідження дозо залежних ризиків виникнення захворювань, є використання адекватного методу дозиметрії, чому присвячений 4-й розділ роботи.

В підрозділі 4.1 висвітлені методичні підходи до оцінки дози опромінення червоного кісткового мозку у випадків лейкемії та підібраних до них контролів.

Метод реалістичної аналітичної реконструкції дози опромінення з оцінкою невизначеності (RADRUE) було обрано із переліку протестованих методів для відновлення дози зовнішнього опромінення на червоний кістковий мозок для субьєктів дослідження лейкемії, або на тканину щитоподібної залози у відповідному проекті.

За результатами проведеного дослідження, було доведено заявлені чутливість і універсальність методу, за допомогою якого було відновлено дози для 112 померлих і для 888 живих суб'єктів дослідження.

Із 162 ідентифікованих випадків лейкемії дозу опромінення вдалось реконструювати тільки для 137 (84.6%).

Центральні оцінки дози на червоний кістковий мозок варіювали від 3.7 10−5 до 3 260 мГр, середня арифметична яких склала 92 мГр., в тому числі для випадків 132,3 мГр і для контролів 81,8 мГр

В підрозділі 4.2 представлено дозиметричні підходи, використані в дослідженні РЩЗ. Зважаючи на те, що в індукції раку щитоподібної залози поряд із зовнішнім опроміненням, суттєву роль може відігравати внутрішнє опромінення цього органу за рахунок інгаляції ^{131}I і короткоживучих ізотопів I і Te , для відновлення цього компоненту дози було розроблено спеціальні математичні моделі, які враховували можливі шляхи надходження названих ізотопів в організм ліквідатора. Необхідність враховувати цей компонент дози зумовила створення відповідних додаткових розділів анкети, які заповнювались під час інтерв'ю із суб'єктами дослідження. Доза зовнішнього

опромінення щитоподібної залози відновлювалась за допомогою метода RADRUE та його модифікації ROCKVILLE.

Дозу опромінення щитоподібної залози за рахунок всіх шляхів опромінення було оцінено для 607 суб'єктів дослідження. Середня арифметична дози опромінення щитоподібної залози, з урахуванням всіх шляхів експозиції, склала 199 мГр (діапазон від 0,15 мГр до 9,0 Гр).

4.1 Українсько-американське дослідження лейкемії і споріднених захворювань серед учасників ліквідації наслідків аварії з України: оцінка дози опромінення червоного кісткового мозку

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The Ukrainian-American Study of Leukemia and Related Disorders among Chornobyl Cleanup Workers from Ukraine: II. Estimation of Bone Marrow Doses

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After the accident that took place on 26 April 1986 at the Chornobyl nuclear power plant, hundreds of thousands of cleanup workers were involved in emergency measures and decontamination activities. In the framework of an epidemiological study of leukemia and other related blood diseases among Ukrainian cleanup workers, individual bone marrow doses have been estimated for 572 cases and controls. Because dose records were available for only about half of the study subjects, a time-and-motion method of dose reconstruction that would be applicable to all study subjects, whether dead or alive, was developed. The doses were calculated in a stochastic mode, thus providing estimates of uncertainties. The arithmetic mean individual bone marrow doses were found to range from 0.00004 to 3,300 mGy, with an average value of 87 mGy over the 572 study subjects. The uncertainties, characterized by the geometric standard deviation of the probability distribution of the individual dose, varied from subject to subject and had a median value of about 2. These results should be treated as preliminary; it is likely that the dose calculations and particularly the uncertainty estimates will be improved in the follow-up of this effort.

INTRODUCTION

The accident that took place on 26 April 1986 at the Chornobyl (Chernobyl)[2] nuclear power plant (ChNPP) located in Ukraine, about 12 km south of the border with Belarus, occurred during a low-power engineering test of the Unit 4 reactor (also called the 4th block of ChNPP) and is the most severe that the nuclear power industry has ever known (*1*). The workers involved in various ways after the accident include (a) the approximately 600 emergency workers who participated in firefighting and other emergency measures during the first day of the accident and (b) the hundreds of thousands of cleanup workers, also called ''liquidators'' or ''recovery operation workers'', who were active in 1986–1990 at the power station or in the 30-km restriction zone surrounding it for decontamination work, sarcophagus construction, other cleanup activities, and the operation of other units of the nuclear power plant. All together, about 600,000 persons (civilian and military) have received special certificates identifying them as cleanup workers, according to laws promulgated in Belarus, the Russian Federation, and Ukraine (*1*). Although the principal tasks carried out by the cleanup workers involved decontamination or construction (*2*), a broad variety of other activities, such as administration and research, infrastructure support (housing, food, transportation), radiation monitoring, communication, security and transportation, were also included.

The most important pathway of exposure for the cleanup workers was external irradiation from the γ-ray emitters deposited on building surfaces (indoors or outdoors) or on the ground. This resulted in a relatively uniform irradiation of the whole body. The external γ-ray doses were measured or estimated, recorded and included in national registries for about half of the liquidators (*3*). However, the quality of these data was not uniform and was often rather low (*4*).

Studies of cleanup workers provide an opportunity to add to current knowledge about the possible health consequenc-

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[2] Standard Ukrainian spellings of place names are used in this paper. The most noticeable differences are for the site of the accident and the nation's capital, Kyiv, but the names of other locations also differ from those used in previously published papers.

FIG. 1. Geographic regions of Ukraine where the 572 subjects resided. The numbers of subjects in each oblast are shown, except for Kyiv, where the number from the city (indicated as ''in Kyiv'') is separated from the total for the remainder of the oblast.

es of exposure to relatively low doses of ionizing radiation received gradually over a period of several months. The Research Center for Radiation Medicine (RCRM) of the Academy of Medical Sciences in cooperation with the Ministry of Health of Ukraine and the U.S. National Cancer Institute (NCI) have conducted a case-control study of leukemia and other related blood diseases involving 572 Ukrainian workers. General features of the method used to estimate the bone marrow doses for the study subjects and the dosimetric results that have been obtained are presented in this paper. Technical details of the method of dose estimation are given in a paper soon to be submitted for publication.[3] Two companion papers, one on the design of the epidemiological study (*5*) and the other on the results of the epidemiological analysis (*6*), are published in this issue.

MATERIALS AND METHODS

Characteristics of the Study Subjects—Dosimetric Perspective

The selection criteria for study subjects included (a) initial registration in the Chornobyl State Registry of Ukraine (SRU) as a cleanup worker residing in Kyiv City or in Cherkasy, Chernihiv, Dnipropetrovsk, Kharkiv or Kyiv oblasts (locations in which approximately 46% of Ukrainian liquidators resided); (b) first year of service from 1986 through 1990; (c) gender (male); (d) age (year of birth between 1926 and 1972); and (e) Chornobyl-related work within the 70-km zone around ChNPP.[4] Subjects were not required to be alive at the time of selection. Detailed information on the design of the study, creation of the cohort, case identification and validation, selection of controls, and tracing and recruitment is provided in ref. (*5*). The subjects who were diagnosed with hematological disease or who served as controls were not identified to the dosimetrists. The distribution of the 572 study subjects according to oblast or city of residence at the time of registration in the SRU is given in Fig. 1; about half of the study subjects originated from Kyiv City and Kyiv Oblast.

The study subjects have been classified into 11 categories according to (a) the period during which they were at the Chornobyl site or (b) their affiliation and thus the type of work performed at Chornobyl. These 11 categories fall into four broader groups reflecting particular characteristics of their involvement into Chornobyl cleanup.

Group 1, early respondents, includes three categories:

1. *Witnesses of the accident* were at the ChNPP site when the accident happened or came there before May 1, 1986, and who were not diagnosed later with acute radiation syndrome (ARS).
2. *Victims of the accident* are the witnesses of the accident who were later diagnosed with ARS.
3. *Early liquidators* are all civilian liquidators (except for ChNPP personnel) who worked within the 30-km zone, including the industrial area of the ChNPP, between April 27 and May 31, 1986.

Group 2, professional nuclear workers, includes four categories:

1. *ChNPP personnel* are the plant staff members who worked between May 1986 and the end of 1990 to conserve and prepare other units of the ChNPP for regular operation.

[3] The working title of the paper to be submitted to Health Physics is ''RADRUE method for reconstruction of external doses to Chernobyl liquidators in epidemiological studies.'' The authors are V. Kryuchkov, V. Chumak, E. Maceika, L.R. Anspaugh, E. Cardis, E. Bakhanove, I. Golovanov, V. Drozdovitch. N. Luckyanov, A. Kesminiene, P. Voilleque and A. Bouville.

[4] Technically, eligibility criteria for being certified as a liquidator include work within the 30-km restriction zone around the ChNPP site in the years 1986–1990. However, in the course of tracing and enlisting the subjects of the study, it turned out that not all officially certified liquidators actually worked within the 30-km zone. Therefore, for the purposes of this study, eligibility criteria were expanded to include work within the 70-km radius around the ChNPP.

TABLE 1
Distribution of the Subjects According to Category and First Year of Work

Category	Total number	Year of beginning of work				
		1986	1987	1988	1989	1990
Group 1: Early respondents						
Witnesses of the accident	3	3				
Victims of the accident	2	2				
Early liquidators	66	66				
Subtotal early respondents	71	71				
Group 2: Professional atomic workers						
ChNPP personnel	9	6	3			
Sent to assist the ChNPP staff	1	1				
Staff of AC-605	5	5				
Staff of Kurchatov Institute	2			1	1	
Subtotal atomic workers	17	12	3	1	1	
Group 3: Uniformed liquidators						
Military liquidators	220	109	49	42	17	3
Subtotal uniformed	220	109	49	42	17	3
Group 4: Other						
Civilians Sent on Mission (CSOM) to the 30-km zone	181	138	32	6	3	2
Staff of Combinat	4		4			
Mixed	79	78		1		
Subtotal other	264	216	36	7	3	2
All	572	408	88	50	21	5

2. *Sent to assist ChNNP* are employees of other nuclear power plants who were sent to assist and temporarily substitute for the regular ChNPP staff at time of recovery and preparation for restart of Units 1–3.
3. *Staff of AC-605* are persons from the organization, named Administration of Construction No. 605, involved in the construction of the shelter covering the damaged reactor.
4. *Staff of Kurchatov Institute* are scientists and engineers from the Kurchatov Institute of Atomic Energy who studied the condition and distribution of the fuel mass inside the Unit 4 reactor building.

Group 3, uniformed liquidators, also called *Military liquidators*, are either regular military or civilian reservists who performed decontamination (e.g., in Unit 4 and on the roofs) and other tasks not requiring skilled labor.

Group 4, other, includes three categories of subjects who do not fall into any of above three groups:

1. *Civilians Sent on Mission* (*CSOM*) are those persons who were sent to perform various tasks in the 30-km zone after June 1, 1986.
2. *Staff of Combinat* are individuals from that organization who performed a variety of tasks in the 30-km zone and coordinated the work of persons sent on mission to the 30-km zone.
3. *Mixed* refers to a set of liquidators who worked on the Chornobyl site several times as members of different categories.

The distribution of the study subjects according to category is presented in Table 1. About two-thirds of the study subjects were either military or CSOM. Most of the study subjects worked at Chornobyl in 1986, with decreasing numbers during the following years (Table 1). It should be noted that, based on our previous studies, we expected that about 50% of liquidators would be military. The lower percentage of military workers among the 572 study subjects (39%) can be explained by the large number of liquidators from the city of Kyiv and Kyiv oblast, who were mostly temporarily assigned specialists sent on mission. Separate consideration of the breakdown of liquidators from the city of Kyiv and Kyiv oblast by different categories compared with the other four oblasts supports this assumption (Table 2). Based on proper weighting, the structure of the whole Ukrainian liquidator population was estimated, yielding results consistent with our previous studies.

It should be noted that 65 study subjects (11%) spent more than 1 year at the site, either on a single mission or on separate missions. Some missions were separated in time, leading to long periods between the beginning and the end of work in the restriction zone (see Table 3). In fact, 133 subjects (23%) had more than one mission; the maximum number of missions was 11 and the average was about 1.4.

Normally only part of the time of a mission to Chornobyl was allocated to cleanup activities. Some time (e.g. while resting, training, waiting for assignment, etc.) was spent in areas with low contamination. Thus a distinction should be made between the total duration of a mission and the number of active days spent at work in relatively high radiation fields. The number of active days is smaller than the total number of days in mission for about 30% of the subjects, averaging 69% of total time. The average active duration was 92 days per mission and 124 days per person (all missions). In total, the 572 subjects spent 2369 man-months of active work in Chornobyl. The distribution of the duration of active work for the study subjects is presented in Fig. 2; Fig. 2a shows the distribution of the active duration of all individual missions, and Fig. 2b illustrates the distribution of the total time spent on active work by the study subjects. The distribution of durations of both missions and total times at Chornobyl is quite broad and, as can be seen from Table 2, varies significantly for different categories.

Status of Dosimetric Information Related to Study Subjects

For about one-quarter of the study subjects, Official Dose Records (ODR, also called ''official doses'') are available in the SRU. The quality of ODR is variable (*3, 4*). Official doses were generally obtained in one of four ways: (a) individual dosimetry measurements, (b) group dosimetry measurements, (c) group dose assessments, and (d) time-and-motion analysis soon after the accident. Civilian workers with individual dose measurements [method (a)] were the staff of AC-605, ChNPP personnel after June 1, 1986, and part of the staff of the organization Combinat. A few military personnel, who worked in locations where the exposure rate was greater than 1 mR h^{-1} were also supposed to have individual dosimeters. For group dose measurements [method (b)], an individual dosimeter was given to one member of a group of cleanup workers assigned to

TABLE 2
Structure of the Liquidator Population in the Study and Reconstruction of the Structure of Whole Liquidator Population in Ukraine

Category	Study population (whole cohort)		City of Kyiv and Kyiv oblast		Other four oblasts		Estimated percentages for the liquidator population from Ukraine
	Number (%)	Median duration of work, days (min, max)	Number (%)	Median duration of work, days (min, max)	Number (%)	Median duration of work, days (min, max)	
Witnesses of the accident	3 (0.5)	7 (1, 11)	2 (0.7)	6 (1, 11)	1 (0.4)	7 (7, 7)	<1
Victims of the accident	2 (0.3)	2 (1, 2)	2 (0.7)	2 (1, 2)	0 (0.0)	— (–, –)	<1
Early liquidators	66 (11.5)	7 (1, 185)	50 (17.1)	7 (1, 185)	16 (5.7)	7 (3, 16)	~10
ChNPP personnel	9 (1.6)	317 (36, 1420)	8 (2.7)	379 (36, 1420)	1 (0.4)	225 (225, 225)	~1
Sent to assist the ChNPP staff	1 (0.2)	31 (31, 31)	1 (0.3)	31 (31, 31)	0 (0.0)	— (–, –)	<1
Staff of AC-605	5 (0.9)	31 (19, 63)	1 (0.3)	24 (24, 24)	4 (1.4)	46 (19, 63)	~1
Staff of Kurchatov Institute	2 (0.3)	157 (138, 175)	0 (0.0)	— (–, –)	2 (0.7)	157 (138, 175)	<1
Military liquidators	220 (38.6)	67 (6, 833)	33 (11.3)	65 (7, 366)	187 (66.7)	69 (6, 833)	48
Civilians Sent on Mission (CSOM) to the 30-km zone	181 (31.6)	19 (1, 1710)	121 (41.5)	18 (1, 1710)	60 (21.5)	21 (2, 103)	28
Staff of Combinat	4 (0.7)	458 (164, 1450)	4 (1.4)	458 (164, 1450)	0 (0.0)	— (–, –)	<1
Mixed	79 (13.8)	250 (4, 1710)	70 (24.0)	258 (4, 1710)	9 (3.2)	111 (9, 1710)	10
All	572		292		280		

perform a particular task, and all members of the group were assumed to receive the same dose. In the group assessment [method (c)], the dose to the whole group of liquidators was assessed by a dosimetrist in advance by considering the exposure rate at the work location and the planned duration of work. Similarly, time-and-motion analyses [method (d)] for more complex tasks were based on measurements of γ-radiation levels at various locations and the individual's dose was estimated using knowledge of the places where he worked and the time spent in these places. Methods (b) and (d) were used for the civilian workers before June 1986, when the number of individual dosimeters was insufficient, and method (c) was used for the majority of the military personnel at all times.

Table 4 shows the fractions of each liquidator category for which ODR are available. Personal interviews revealed that many liquidators possess information on doses (like dose certificates or records in military ID book) that is not included in the SRU. This is not surprising because the ODR in the SRU were derived from documents provided personally by liquidators at the time of primary registration. Some liquidators did not have such dose documents at the time of primary registration and obtained them only after being registered in the SRU.

Victims and witnesses of the accident, early liquidators sent to the 30-km zone, and others did not have measured doses because the personal dosimetry system in use at the early time after the accident had failed (*4*). During the 1990s, doses from external irradiation were reconstructed using a time-and-motion method called Analytical Dose Reconstruction (ADR). This technique was used to estimate doses to the staff of ChNPP and workers who had been detailed to assist them for the period from 26 April to 5 May 1986 (*2*). Personnel location record cards (route lists) filled in by workers and confirmed by eyewitnesses were analyzed by experts who had reliable information on the radiation conditions and who had personally participated in ensuring the radiation safety of all operations after the accident. Using this method, two doses were estimated: an upper bound dose and an expected dose. The upper bound doses ranged from less than 100 mGy to a few thousand mGy and were estimated to be about twice the expected doses (*2*).

TABLE 3
Distribution of Subjects According to Time of Work

First year of work	Number of subjects					
	Year of completion of work					
	1986	1987	1988	1989	1990	All
1986	291	50	20	11	36	408
1987		63	16	4	5	88
1988			46	4		50
1989				18	3	21
1990					5	5
1986–1990	291	113	82	37	49	572

Other available sources of dosimetric information, such as the archives of the Ministry of Defense or the dosimetry databases that were acquired during the course of the study, provided information for only a limited number of subjects. It was found that dosimetric information (total individual doses and, in some cases, daily or monthly doses) in the archives of the Ukrainian Ministry of Defense had been stored in paper form and was not linked with the SRU, while individual dose values were recorded in the personal military certificates possessed by all military liquidators and had already been entered into the SRU at time of registration. Information from the military archive was entered into a computer database. This facilitated a comparison of these data with ODRs in the SRU, which revealed large overlap of information and good coincidence of individual dose records from these two files. Therefore, inventory and data entry of the military archives added little to the already existing information on individual dose records of military liquidators. The individual dosimetric monitoring (IDM) databases were also of little use because only a small fraction (17,754 out of about 168,000) of dose records in the IDM databases had sufficient identifiers (full names, year of birth) and the liquidators to whom these records were related were identified only as residing in Ukraine. Moreover, only 1,893 records (out of 17,754 possessing necessary keys) were linked with certainty with the SRU, adding 1,613 new dosimetric data entries previously missing in the Registry (*7*).

Development of the Routine Dose Reconstruction Method; Its Principles and Application

The methods of dose estimation discussed above are very different in nature and are applicable to differing fractions of the study subjects. In addition, some of the methods lead to results that cannot be easily verified. Therefore, it was necessary to develop a universal method of dose

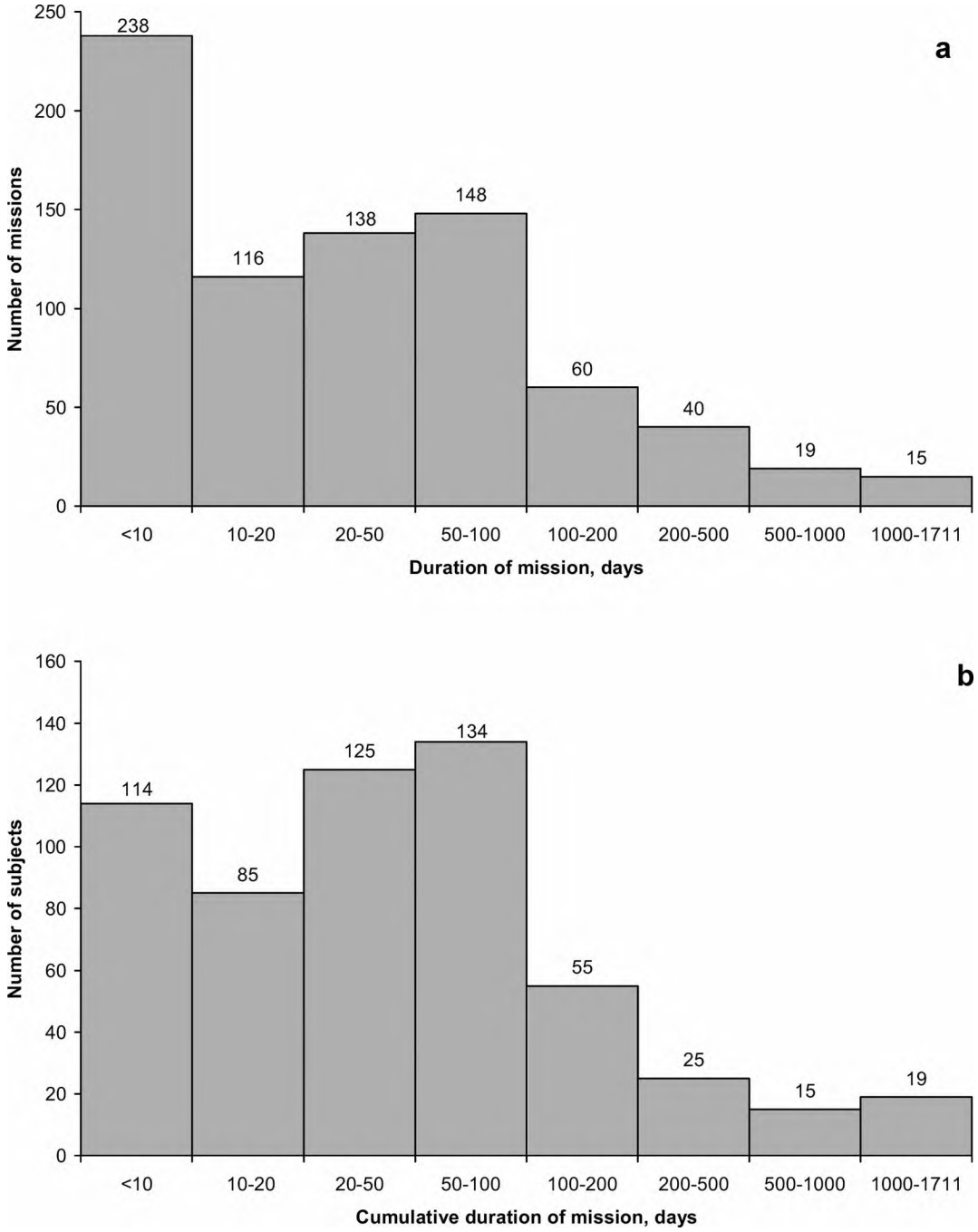

FIG. 2. Distribution of times (active days) spent in Chornobyl: (panel a) individual missions and (panel b) cumulative periods of work. The maximum possible duration of work in Chornobyl was 1711 days, corresponding to the number of days within the period from April 26, 1986 to December 31, 1990.

estimation that would be (a) applicable to all subjects, whether deceased or alive, and (b) based on information that would be relatively easy to process and to check.

The task of selection or development of the universal dose assessment method, applicable to all subjects of the study, was addressed during the pilot phase of the project (1996–2000). Readily available techniques like ADR, EPR (electron paramagnetic resonance) dosimetry with teeth, and FISH (fluorescence *in situ* hybridization) using chromosomes in human lymphocytes were considered from the point of view of the above criteria and were found to be inadequate for the purposes of the study. An overview of the methods of dose reconstruction evaluated during the feasibility study is given in Table 5. It can be seen that biodosimetry and instrumental methods depend on the availability of specimens (blood or teeth) and have sensitivity thresholds that are not always compatible with anticipated doses to liquidators. Both these methods have the disadvantage of measuring total dose, including components due to medical exposures or to occupational exposures other than those received during Chornobyl cleanup work.

Analytical techniques, which rely on the results of interviews with liquidators, do not have a dose threshold and can be applied to virtually all subjects, both alive and deceased. In the latter case, a proxy for the subject can be interviewed to collect the necessary information regarding

TABLE 4
Number of Study Subjects with Official Doses Records (ODR) in the Registry and with ODR in their Possession

Category	Number of subjects	Number of ODR	Percentage in registry	Number of doses in personal records[a]	Percentage in personal records
Witnesses of the accident	3	0	0%	1	33%
Victims of the accident	2	0	0%	1	50%
Early liquidators	66	4	6%	7	11%
ChNPP personnel	9	0	0%	3	33%
Sent to assist the ChNPP staff	1	0	0%	0	0%
Staff of AC-605	5	1	20%	3	60%
Staff of Kurchatov Institute	2	2	100%	1	50%
Military liquidators	220	106	48%	174	79%
CSOM to the 30-km zone	181	11	6%	14	8%
Staff of Combinat	4	0	0%	2	50%
Mixed	79	1	1%	13	16%
Total	572	125	22%	219	38%

[a] Data acquired in course of interview include dose certificates possessed by subjects.

the activities of the subject in the radiation zone. However, the readily available ADR technique had several shortcomings that prevented it from being applied routinely to the subjects of this study. First, the ADR route lists required a high degree of precision and specificity (supported by witness reports), so only a few highly skilled and motivated liquidators were capable of providing the necessary information. The general liquidator population, many of whom performed unskilled work without personal initiative, could not describe their activities sufficiently. The second limitation of ADR was that the dose calculations were designed to overestimate the received doses. This was due to a ''radiation protection approach'' in which longer exposure times and higher dose rates were normally selected to avoid underestimating the dose received. This qualitative effect was confirmed in comparisons with individual dose estimates obtained using EPR analysis of tooth enamel (*8*). Given the shortcomings of the ADR method, a new method called SEAD (Soft Expert Assessment Dosimetry) was designed (*9*). The procedure used interview data and dose distributions for each liquidator category to assess the individual dose received by the liquidator according to a set of objective and subjective parameters. This conceptually non-trivial methodology uses fuzzy-set algebra for uncertainty propagation. In addition, reliable dose distributions needed to implement the method for each worker category were not available. In view of these limitations, the SEAD method was not considered to be applicable to all study subjects.

In view of the limitations of the approaches discussed above, a new time-and-motion method, known as Realistic Analytical Dose Reconstruction with Uncertainty Estimation (RADRUE), was developed by an international group of scientists including experts from Belarus, France, Russia, the U.S. and Ukraine.[5] The RADRUE method was conceived for this study as well as for International Agency for Research on Cancer (IARC) studies of Baltic, Belarusian and Russian cleanup workers. It is based on a detailed analysis of the liquidator's activities during cleanup, including all places of work and residence, types of work, transportation, etc. This information is combined with data on the radiation fields at the locations and dates where the liquidator spent any time to reconstruct a history of the radiation exposures received during the period when the liquidator was involved in cleanup activities. Although RADRUE can be considered to be a further development of ADR, there are fundamental differences between the methods. First, universal application of RADRUE to all study subjects was achieved by simplification of the questionnaire. In the RADRUE method, activities and movements of liquidators are described in more general terms with fewer details. Because the information requested is less specific, the questionnaire can be administered both to living subjects and to proxies (coworkers and next of kin) for subjects who are deceased. Most importantly, estimates of residence times and exposure rates are intended to be realistic and to provide central, rather than conservative, estimates of doses received by Chornobyl liquidators.

Within the Ukraine-U.S. study, special sub-studies were designed and performed for different liquidator categories (e.g. military and CSOM) and helped to refine the RADRUE methodology (*8*). The high-precision EPR dosimetry technique with teeth developed in the RCRM (*10*) was used as the main reference method for checking doses estimated using the RADRUE technique. All comparisons of RADRUE dose estimates with the reference dose values were analyzed rigorously and used for refinement of the technique.

Some dose estimates obtained using the unrefined RADRUE method were found to overestimate doses actually received by groups of cleanup workers whose exposures were controlled by the radiation protection staff of the group. The exposures of these workers were routinely monitored and limited according to applicable guides, such as daily dose limits, established for the organization. Three worker groups operated under some version of dose control: military liquidators who worked in an organized team, the staff of the ChNPP, and the staff of the AC-605 construction organization. The RADRUE method was modified to include an evaluation of whether such dose limitation should be reflected in the estimate for a particular subject. The key components of the evaluation were (a) whether the individual was in one of the three groups of workers and (b) whether the same daily activity was repeated three or more times.

A second important refinement of the method was implementation of new techniques of handling uncertain itinerary data. In the revised approach, three options are provided to reflect the differing levels of detail provided by subjects. If the subject provides a specific sequence of movements to specific locations, the path defined by the subject is used for

[5] The International Dosimetry Group included at different times the following persons: Dr. Andre Bouville (NCI, USA), Dr. Lynn Anspaugh (University of Utah, USA), Dr. Geoff Howe (Columbia University, USA), Dr. Elisabeth Cardis, Dr. Ausra Kesminiene and Dr. Evaldas Maceika (IARC, France), Dr. Philippe Hubert and Dr. Margot Tirmarche (Institute of Radioprotection and Nuclear Safety, France), Dr. Viktor Kryuchkov and Mr. Ivan Golovanov (Institute of Biophysics, Russia), Prof. Viktor Ivanov, Dr. Valery Pitkevich (Medical Radiological Research Center, Russia), Dr. Anatoly Mirkhaidarov (Institute of Radiation Medicine, Belarus), Mr. Sergey Illychev, Mr. Alexander Tsykalo, Mr. Viktor Andreev, Mr. Viktor Glebov (ChNPP, Ukraine), Dr. Vadim Chumak, Dr. Natalia Gudzenko and Dr. Elena Bakhanova (RCRM, Ukraine).

TABLE 5
Methods of Dose Assessment that were Considered in the Feasibility Study but Not Approved for Routine Dose Reconstruction

Method	Source of information/ type of sample	Sensitivity threshold	Applicability	Reason for rejection
Analytical Dose Reconstruction (ADR)	Interrogation after exposure, witness confirmation	No threshold	Not universal	Applicable only for highly skilled ChNPP employees, tends to overestimate actual dose
Electron paramagnetic resonance (EPR) dosimetry with teeth	Teeth extracted for medical reasons	50 mGy	Not universal	Applicable only for tooth donors; useful dose range only partially matches liquidators' dose range
Fluorescence *in situ* hybridization (FISH)	Blood samples	250–300 mGy	Universal for living subjects	Useful dose range does not match the dose range for most liquidators
Soft Expert Assessment Dosimetry (SEAD)	Interview	No threshold	Universal	Conceptually non-trivial, bad results of testing for some categories of liquidators

dose estimation. If the locations, but not the sequence, are given, then the average dose rate for the activity is more uncertain. The least definite description is when only the work area is recalled, which leads to the greatest uncertainty in dose estimation.

The latest version of RADRUE incorporates these improvements and is the one used to make the dose calculations for the study subjects. Prior to implementation for the study, the RADRUE calculations were compared with other reliable dose estimation techniques that were applied to workers who received a wide range of doses. Victims and witnesses of the accident received the highest doses; estimates based on dicentric chromosome aberration frequencies in 20 persons covered a dose range of 200–14,000 mGy, with most doses above 1,000 mGy. Comparisons showed that RADRUE estimates were comparable but somewhat (~20%) lower than those based on unstable aberrations. For a group of workers carefully monitored using TLDs, the dose range was 1–190 mGy and ratios of RADRUE to TLD doses ranged from 0.5 to 3.6, with a median value of ~1.4. A third set of RADRUE estimates was compared with dose estimates based on EPR in the dose range 50–200 mGy; the median dose ratio was close to unity, with values lying within a range of 0.26–3.9. These comparisons showed that the RADRUE estimates were not highly biased in either direction.

Spatial and Temporal Variations of Exposure Rates[6]

A key element of the time-and-motion approach employed by RADRUE is knowledge of the radiation exposure rates at the locations where the liquidators lived and worked during their stays in the vicinity of the Chornobyl facility. The radiation exposure rates in the 30-km zone around Unit 4 of the ChNPP varied substantially in space and time after the accident. Spatial variations were due to (a) complex deposition patterns that reflected conditions during the period when most releases occurred, (b) localized hot spots where reactor core debris and/or pieces of highly radioactive equipment landed, and (c) local exposure-rate extrema produced by unshielded beams of radiation passing through fractures in reactor shielding. The temporal variations of exposure rates were caused by (a) the continuing radioactivity release (especially for the first 10 days to 1 month after the accident), (b) radioactive decay of deposited materials, and, later, (c) the effects of massive decontamination activities conducted within the 30-km zone. For the purposes of dose estimation using the RADRUE method, all available exposure-rate measurement data were inventoried, checked for consistency, and compiled according to location and time of measurement. These measurements were supplemented by measurements of deposition densities of specific radionuclides that could be used to estimate exposure rates. The available information was interpolated in space and time to generate standardized data sets for areas of interest during the 4.7-year period when subjects were exposed.

Figure 3 gives a snapshot of the exposure-rate pattern over the ChNPP industrial site 30 days after the accident and illustrates the wide range of values encountered. (One should note that the RADRUE exposure-rate database operates with the maps of different scales that are related to particular ''geographical'' areas. In Fig. 3, the exposure rate isolines are only given for the ''Industrial site of the ChNPP'' map. Although this area also includes ''Roofs of ChNPP'' and ''The main building of ChNPP'', the map scales differ and isolines of those exposure-rate maps are not shown.) Figure 4 shows the time dependence of measured and estimated exposure rates for a location close to the ChNPP Units 3 and 4. The estimated minimum, mean and maximum values used in dose calculations by RADRUE are shown in the figure. Effective γ-ray energies for the radiation fields encountered were in the range 100–500 keV and depended on the contamination level (in general) and any peculiar features affecting the exposure location.

Practical Considerations of RADRUE Application

RADRUE is a complex technique containing many specific aspects and features. In this paper, only the features of RADRUE that are specific to the Ukrainian-American case-control study of leukemia and other related blood diseases are presented and discussed. A separate paper (see footnote 3) is devoted to a more detailed description of the technical aspects of RADRUE as used in both the Ukrainian-American and the Belarus/Baltic/Russia/IARC studies.

The implementation of RADRUE is a multi-stage process; the main steps are presented schematically in Fig. 5. This process engages various specialists, including interviewers, data registration operators and coders, expert dosimetrists, and developers of the RADRUE technique and dose calculation code. Some significant features of this process are discussed below.

1. Interviews

Persons who conducted interviews within the Ukrainian-American study were carefully selected and trained. They were themselves liquidators who had a detailed knowledge of the 30-km zone and of the cleanup work that was conducted after the accident. They conducted personal interviews with the liquidator himself, if he was alive and not incapacitated, to obtain descriptions of his Chornobyl work and other activities. Approximately 15% of the study subjects were deceased (*5*). For the 76 deceased and two incapacitated study subjects, interviews were carried out with proxy respondents. Two types of proxies were selected for each deceased subject: a spouse or next-of-kin proxy to provide data on demographic factors and medical history and one or several coworker prox-

[6] At the time of the Chornobyl cleanup work in 1986–1990, all the radiation measurement devices used for monitoring were calibrated in terms of exposure rate (mR h^{-1}), and it is therefore convenient to use exposure rates (in those units) in the retrospective dose calculations.

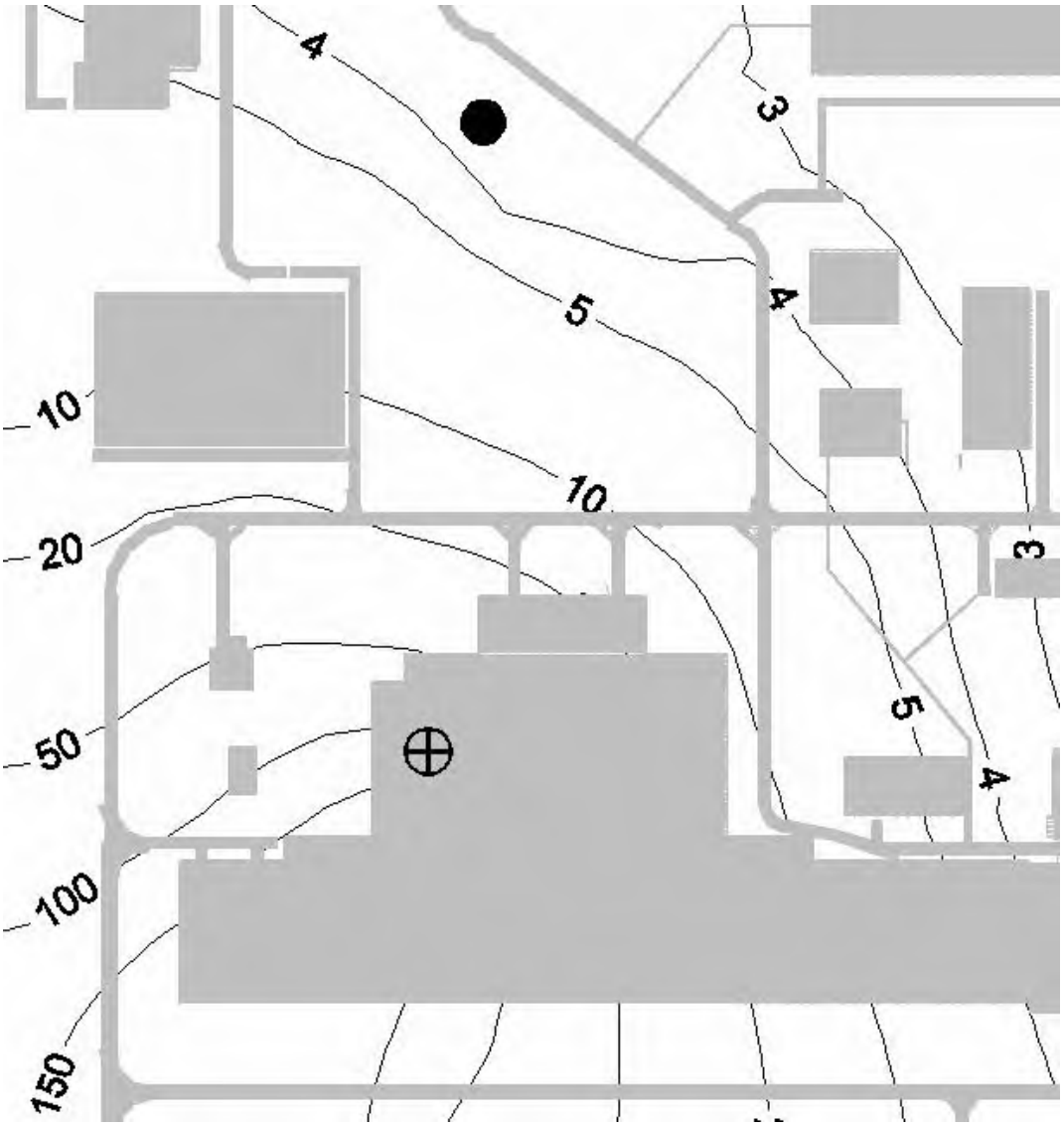

FIG. 3. Spatial pattern of exposure rates (R h^{-1}) at the ChNPP industrial site on May 26, 1986. Position of reactor No. 4 is marked with crossed circle; the location of the point considered in Fig. 4 is marked with shaded circle. Gray objects represent NPP buildings and roads.

ies (usually nominated by the spouse) to provide information on the deceased liquidator's experience at Chornobyl. This would include military unit (if applicable), temporary residence location, type of activities, and duration of work as a liquidator.

2. *Registration and scanning of questionnaires. Role of the Data Coordination Center*

All processes of document turnover are conducted under supervision of the Data Coordination Center (DCC). Completed questionnaires were registered in DCC and then dispatched for scanning into computer graphical files, coding of the responses, and entry into the computer database. Information essential for classification of liquidators, was extracted into a special form called the dosimetric synopsis. This form was also used for recording the expert's evaluation of completeness and trustworthiness of the interview data. Data from the dosimetric synopsis were used for classification and categorization of the study subjects. The DCC coordinated all stages of the questionnaires processing and provided participants with the auxiliary information (e.g., affiliation, non-Chornobyl occupational history, health records, etc.). Results of simulation (arithmetic and geometric means, standard and geometric standard deviations as well as 10,000 random realizations of dose; see below) are also stored at the DCC to be used in further epidemiological analysis.

3. *Roles of the experts*

Relatively general questionnaires (see Supplementary Information) completed during the personal interview were processed by the expert dosimetrists. Their task was to reconstruct the itinerary followed by the liquidator and to provide information on the uncertainties associated with the itinerary, including alternative options, when applicable. An expert must have unique skills. He must be extremely familiar with the history of Chornobyl cleanup activities, including the sequence and duration of the main activities in the 30-km zone, and with the geography of the area. He must be aware of radiation protection issues and, for example, know the routes of movement and transportation usually chosen to minimize doses. Within this study, two experts were qualified and trained for this role. Both were long-time employees of the radiation safety department at the Chornobyl NPP and were actively involved in the Chornobyl cleanup over several years after the accident. In the course of their work, they

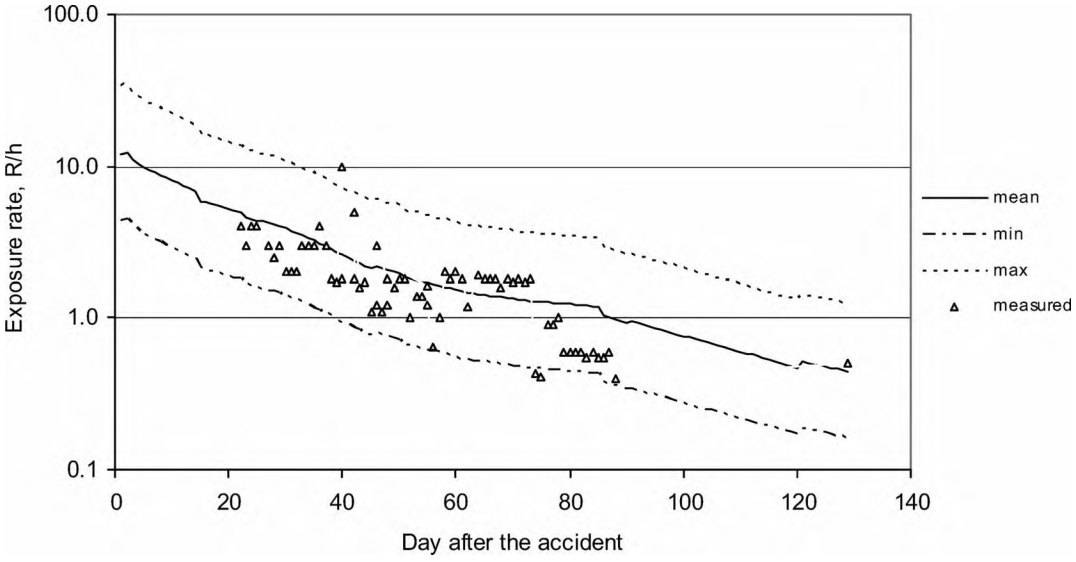

FIG. 4. Time course of exposure rate (R h^{-1}) at the ChNPP industrial site. Triangles mark measurement data, the solid curve the estimated mean dose rate in this area, and the dashed lines the estimated maximum and minimum exposure rates for this area. See Fig. 3 for the location of the measurement point.

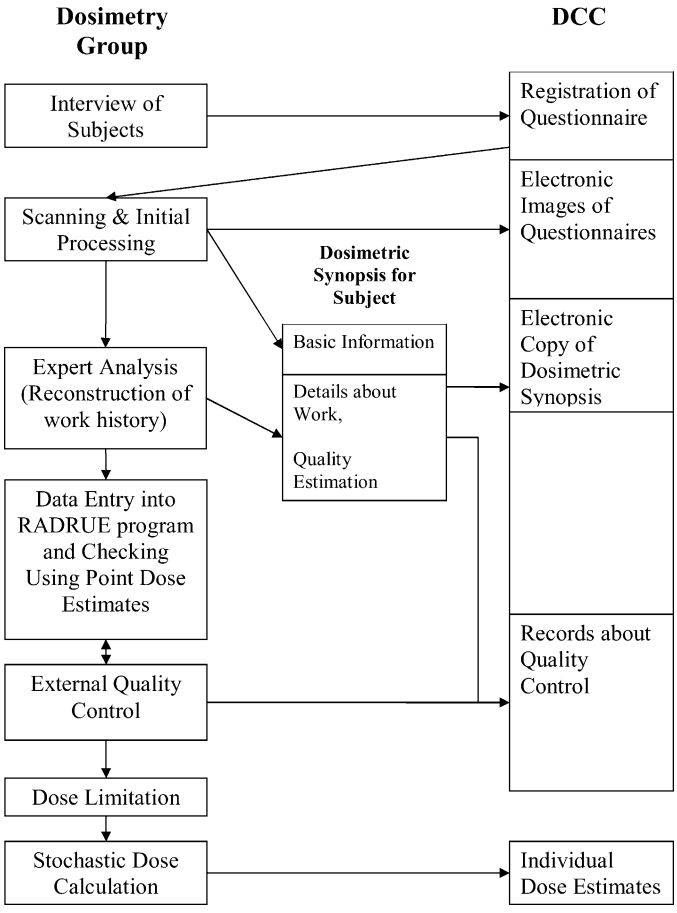

FIG. 5. Flow chart of dose reconstruction using RADRUE. DCC is the acronym for the Data Coordination Center. The dose limitation procedure applies only to liquidators in certain groups who performed tasks repetitively (see the text).

used archives related to Chornobyl chronicles and consulted with persons in charge of cleanup activities. This auxiliary information was used for verification of the questionnaire data and reconstruction of a liquidator's itinerary based on information available from the questionnaire. Summarized information about the work history is entered into the dosimetric synopsis.

The work of the experts was reviewed independently. The reviewer examined the expert's interpretation of the questionnaire responses for each subject. Additionally, the reviewer made independent dose estimates for about 5% of the subjects, and his results were compared with those of the expert. For about 5% of the subjects, the two experts analyzed the same questionnaire independently and estimated the doses received. The independent dose calculations were compared (reviewer and expert, expert 1 and expert 2) and were found to be in good agreement.

The experts were also asked to evaluate the completeness (quality) and trustworthiness of the questionnaires according to five- and four-grade scales, respectively. The first attribute refers to the success of the interviewer in obtaining the desired information, and it naturally reflects the recall of the liquidator (or proxy) as well. The assessment of trustworthiness relates to the plausibility of the reported activities and whether the report is credible or embellished. These grades were entered by experts into the dosimetric synopsis and were recorded in the DCC in a separate database for possible consideration in the evaluation of uncertainties.

Consideration of Uncertainties

Uncertainties of doses estimated by RADRUE technique can be divided into two categories referred to as intrinsic uncertainties and human factor uncertainties. In the first category are uncertainties in exposure-rate data and soil contamination measurements, uncertainties in the interpolation of these data in time and space, uncertainties in location factors used to characterize the effectiveness of shielding, and imprecision of data from the questionnaire (e.g., failure to recall the specific time of a particular mission expressed in indication of some broad time interval instead of specific dates), even though the latter could have been included in the human factor uncertainties. Some of these can be categorized as errors that are shared by subgroups in the cohort or by the entire group. Although there is little overlap in dose for multiple workers experiencing the same exposure rate at the same time, the process of development of the exposure-rate grids is a common element of the dose calculations.

TABLE 6
Ranges of Estimated Bone Marrow Doses and Uncertainties for each Liquidator Category

Category	Number of subjects	Arithmetic mean bone marrow dose (mGy)			
		Average	Minimum	Maximum	Average GSD[a]
Witnesses of the accident	3	160	38	377	2.3
Victims of the accident	2	2880	2580	3170	3.4
Early liquidators	66	97	0.48	1010	2.0
ChNPP personnel	9	234	23	966	1.7
Sent to assist the ChNPP staff	1	44	44	44	1.9
Staff of AC-605	5	110	1	295	2.0
Staff of Kurchatov Institute	2	129	15	242	2.7
Military liquidators	220	71	0.01	554	2.1
CSOM to the 30-km zone	181	30	0.000037	694	2.0
Staff of Combinat	4	16	3	45	1.7
Mixed	79	164	0.40	3260	1.7
All	572	87	0.000037	3260	2.0

[a] Only the intrinsic uncertainty is considered. The average GSD shown for each category is the arithmetic mean of the GSDs of doses for subjects in that category.

In the second category are blunders in responses to questions, particularly by worker proxies, the recording of those responses by the interviewers, and the interpretation of the information by the expert. Variations in analysis between the two experts are included in the ''human factors'' category as well. Initial investigations of human factor uncertainties were performed as special studies. These included evaluation of proxy-interview variability, repeated interviews of individual liquidators, and repeated analysis by the second expert. On the basis of these studies, the human factor component of uncertainty was only qualitatively characterized as ''large'', especially when proxy responses are used in the dose calculations.

A detailed analysis of shared and unshared errors has not yet been performed. The geometric standard deviations reported in the next section reflect an elementary Monte Carlo approach for the intrinsic uncertainties. Repeated calculations in which parameter values are selected randomly from distributions of individual parameters (e.g. dose rates, times, location factors) produce a distribution of doses for each subject. The results from 10,000 trials are summarized in terms of arithmetic mean, geometric means and geometric standard deviations (GSDs) of the output dose distributions.

RESULTS AND DISCUSSION

The results of the dose evaluations for liquidators in the Ukrainian-American study are presented in the following subsections. The first deals with the dosimetry interview process. Then the dose estimates for subjects are summarized and the checks on those estimates are described. Finally, plans for improvement of the method are indicated.

Experts' Evaluation of Questionnaires

The experts judged 91% of the liquidators' questionnaires as ''reliable'' (highest grade of trustworthiness), while only 3% were considered ''unlikely.'' As for the quality of questionnaires, grades of ''excellent'', ''good'' and ''fair'' were given to ~31%, ~39% and ~29%, respectively. The lowest grade was assigned to fewer than 2% of the questionnaires. Quality of interviews measured by average grades did not depend on year of cleanup activity by a subject and was comparable for different interviewers and dates of interview. Ratings of data quality were in general higher for subjects than for proxies. These results indicate that, with few exceptions, subjects provided valid information. They also indicate that training of the interviewers was uniformly effective and that, in general, they all performed well.

Bone Marrow Dose Estimates for Subjects

The RADRUE methodology was applied to estimate bone marrow doses for the 572 subjects of the study, including 71 cases and 501 controls. Both annual and cumulative doses over the entire period of work were calculated. For 76 deceased and two incapacitated subjects, interviews were performed with proxies. Results of dose estimation were delivered to the Data Coordination Center of the project and were used in the epidemiological analysis (*6*). The ranges of estimated doses and uncertainties for each liquidator category are presented in Table 6. For each category the average, minimum and maximum values of the mean doses to individuals are presented for each group. The uncertainty in the dose estimate for each subject is expressed individually as the GSD of the stochastic dose distribution obtained. The last column of the table gives the average value of the GSDs of the dose estimates for members of each category of study subjects. As noted above, the uncertainties of intrinsic type in the dose estimates reflect the uncertainties in the routes and in parameters used in the dose calculations. The distribution of the GSDs for all study subjects is shown in Fig. 6. Information about the collective and annual doses for each liquidator category and first year of work is presented in Tables 7 and 8, respec-

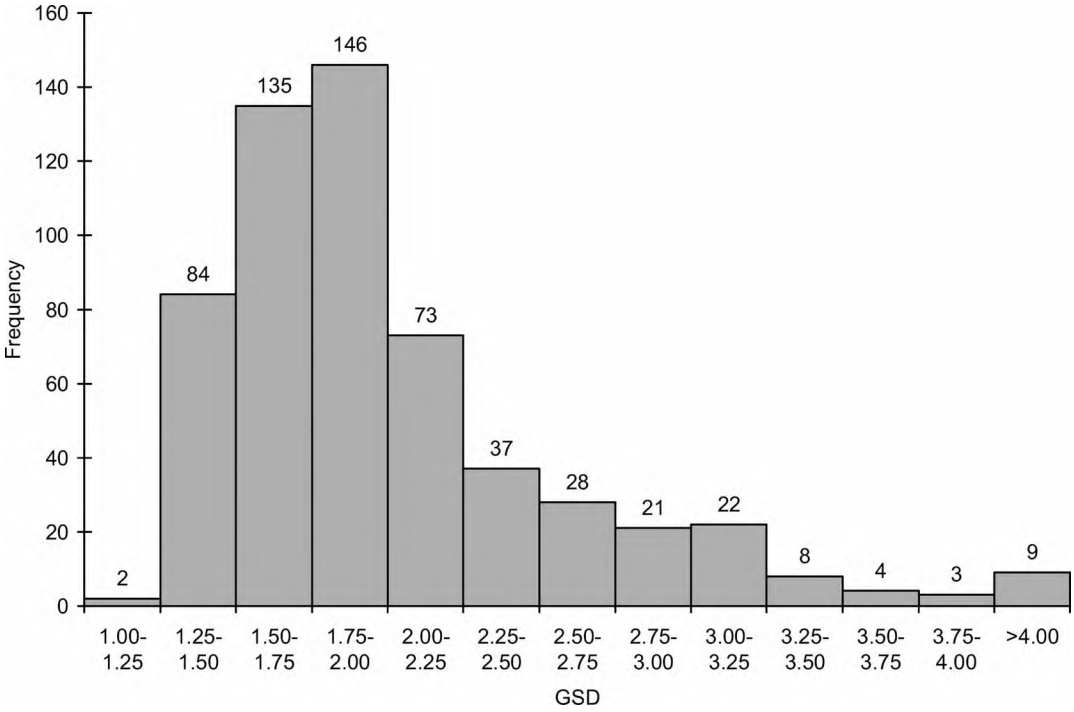

FIG. 6. Distribution of the geometric standard deviations (GSDs) of the bone marrow doses of the subjects.

tively, while average dose estimates for all study subjects according to time of work are presented in Table 9. As shown in Fig. 7, the cumulative dose estimates for these individuals cover a broad range, which is not surprising considering the wide variety of mission durations and types of tasks performed by the liquidators. The range of values seen is illustrated in the following discussion.

Consistency Checks and Validation of the Data

The critical analysis of the dose estimates included various kinds of consistency checks and, in particular, an independent consideration of the highest and lowest doses in each category of workers. The lowest and highest doses estimated for individuals in any category are considered below:

1. The lowest dose to a person sent on a mission to the 30-km zone was 0.00004 mGy. This individual flew in an airplane over the 30-km zone at an elevation of 600 m. The exposure rate calculation for this person required a special calculation that considered both the distance and the shielding provided by the plane.

TABLE 7
Collective Annual Bone Marrow Doses (person-Gy) According to Liquidator Category[a]

	Collective bone marrow dose (person-Gy)				
	First year of work				
Category	1986	1987	1988	1989	1990
Witnesses of the accident	0.48				
Victims of the accident	5.76				
Early liquidators	6.42				
ChNPP personnel	1.90	0.20			
Sent to assist the ChNPP staff	0.04				
Staff of AC-605	0.55				
Staff of Kurchatov Institute			0.01	0.24	
Military liquidators	9.92	3.70	1.28	0.61	0.17
CSOM to the 30-km zone	4.43	0.90	0.02	0.03	
Staff of Combinat		0.06			
Mixed	12.96		0.02		
All	42.46	4.87	1.33	0.88	0.17

[a] See Table 1 for the numbers of subjects in each category.

TABLE 8
Mean Annual Bone Marrow Doses (mGy) According to Liquidator Category[a]

	Mean bone marrow dose (mGy)				
	First year of work				
Category	1986	1987	1988	1989	1990
Witnesses of the accident	160				
Victims of the accident	2880				
Early liquidators	97				
ChNPP personnel	317	67			
Sent to assist the ChNPP staff	44				
Staff of AC-605	110				
Staff of Kurchatov Institute			15	242	
Military liquidators	91	76	30	36	57
CSOM to the 30-km zone	32	28	4	9	0.05
Staff of Combinat		16			
Mixed	166		17		
All	104	55	27	42	34

[a] See Table 1 for the numbers of subjects in each category.

TABLE 9
Averages of Arithmetic Mean Bone Marrow Doses (mGy) According to Time of Work[a]

First year of work	Average arithmetic mean bone marrow doses (mGy)				
	Year of completion of work				
	1986	1987	1988	1989	1990
1986	95	41	128	215	221
1987		49	62	155	35
1988			28	12	
1989				48	7
1990					34
All	95	46	59	105	169

[a] See Table 3 for the numbers of subjects in each category.

2. The highest dose calculated for any study subject was 3300 mGy for one of the individuals in the ''mixed'' category of liquidators. About 95% of his estimated dose was received as an early liquidator, when he reported multiple visits to the industrial site to perform work. At that time, the exposure rates at industrial site locations were high, and the total dose estimated for this individual reflects that fact. Experts reviewing the reported information suspect that the individual overstated the number of visits to the industrial site. Nonetheless, the dose was calculated using the information provided by the subject and is thus likely to be an overestimate. The dubious nature of the information in answers found in this particular questionnaire was indicated in the expert dosimetrist's report and was reflected in a low grade of trustworthiness (grade 2 of 4).

An indirect check on the validity of a high individual dose estimate can be the review of the medical information to see whether the person was diagnosed as having ARS. Symptoms of ARS are expected to occur for absorbed doses in excess of 1.5–2.0 Gy. All together, RADRUE dose estimates for three subjects in the study exceeded this threshold. One person (dose 2600 mGy) was known to have second-degree ARS and was initially classified as a victim of the accident. Closer consideration of the case with a dose estimate of 3200 mGy revealed that the subject was a ChNPP employee who worked there the night of the accident. He was evacuated to Moscow Hospital no. 6 on April 27 and was diagnosed with the second-degree ARS. The person died in 1998; according to his widow, his estimated ''dose'' was about 3000 mGy. Therefore, the observed clinical effects support the high dose estimates for these two victims of the accident. The medical record of the subject with the highest, but dubious dose estimate of 3300 mGy (case 2 above) did not include an established ARS diagnosis. This observation supports doubts concerning the trustworthiness of the interview data in this particular case.

Planned Improvements

Data obtained not from liquidators but from proxies can be a major source of uncertainty. Although the central estimate for the whole group of proxies seems to be unbiased, individual deviations from the ''true dose'' can be extremely large. The arithmetic mean dose estimates for subjects whose doses are based on proxy responses could therefore be increased by a substantial factor because of uncertainties in those responses.

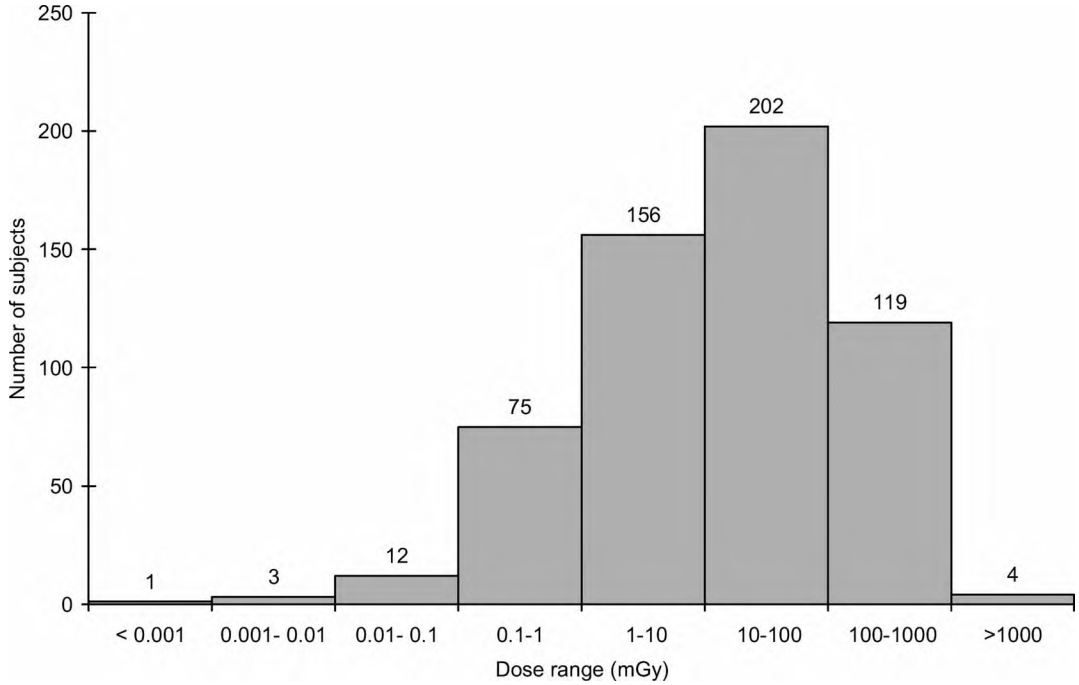

FIG. 7. Distribution of the bone marrow doses for all subjects.

Plans are being made to assess the full extent of the uncertainties (shared and unshared components of intrinsic uncertainties and the human factor uncertainties) related to the current dose estimates and to look for ways to reduce the overall uncertainties as much as possible for future calculations.

SUMMARY AND CONCLUSIONS

The reconstruction of bone marrow doses for the subjects of a case-control study of leukemia in Chornobyl cleanup workers from Ukraine illustrates a systematic approach to dosimetric support of an epidemiological study. This effort included the investigation of the available information on individual doses and the study of the feasibility of finding an existing technique or inventing a new method of dose reconstruction that could be applied to all study subjects. As a result of this pilot phase, a new method called RADRUE was developed. The developmental stage of RADRUE included testing against reference dose estimates (results of dosimetric monitoring for professional atomic workers and EPR dosimetry with teeth for other categories of liquidators), which provided feedback to guide modification and refinement of the RADRUE technique.

The dose reconstruction process includes several stages, namely, questioning of a liquidator or a proxy by a trained interviewer, analysis of the questionnaire by an expert and conversion to RADRUE program input, deterministic and stochastic calculations, and a post-calculation phase, which included comparison with other available data on personal exposure. To obtain necessary information regarding movements and behavior of the subjects, a group of interviewers was hand picked and trained to administer a special questionnaire developed for studies of liquidators.

Doses to 572 subjects of the study were reconstructed, including 494 subjects who were alive and 78 deceased or incapacitated for whom proxies were interviewed. The subjects of the study represent all categories of liquidators, with dominance of military (39%) and CSOM (32%). It should be noted that both locations of work and durations of activity in Chornobyl vary significantly. As a result, doses to study subjects vary over seven orders of magnitude from virtually natural background level to life threatening. The pool of study subjects is a good representative sample of the whole liquidator population.

SUPPLEMENTARY INFORMATION

Study of the Health Status of Liquidators. Subject Questionnaire. Revised 08/2001. http://dx.doi.org/10.1667/RR1403.1.S1.

Study of the Health Status of Liquidators. Co-worker Questionnaire. Revised 08/2001. http://dx.doi.org/10.1667/RR1403.1.S2.

Study of the Health Status of Liquidators. Spouse (or Relative) Questionnaire. Revised 08/2001. http://dx.doi.org/10.1667/RR1403.1.S3.

ACKNOWLEDGMENTS

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4.2 Оцінка доз опромінення для випадок-контроль дослідження раку щитоподібної залози серед українських учасників ліквідації наслідків аварії на Чорнобильській АЕС

Paper

ESTIMATION OF RADIATION DOSES FOR A CASE-CONTROL STUDY OF THYROID CANCER AMONG UKRAINIAN CHERNOBYL CLEANUP WORKERS

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Abstract—**Thyroid doses were estimated for 607 subjects of a case-control study of thyroid cancer nested in the cohort of 150,813 male Ukrainian cleanup workers who were exposed to radiation as a result of the 1986 Chernobyl nuclear power plant accident. Individual thyroid doses due to external irradiation, inhalation of ^{131}I and short-lived radioiodine and radiotellurium isotopes (^{132}I, ^{133}I, ^{135}I, ^{131m}Te, and ^{132}Te) during the cleanup mission, and intake of ^{131}I during residence in contaminated settlements were calculated for all study subjects, along with associated uncertainty distributions. The average thyroid dose due to all exposure pathways combined was estimated to be 199 mGy (median: 47 mGy; range: 0.15 mGy to 9.0 Gy), with averages of 140 mGy (median: 20 mGy; range: 0.015 mGy to 3.6 Gy) from external irradiation during the cleanup mission, 44 mGy (median: 12 mGy; range: ~0 mGy to 1.7 Gy) due to ^{131}I inhalation, 42 mGy (median: 7.3 mGy; range: 0.001 mGy to 3.4 Gy) due to ^{131}I intake during residence, and 11 mGy (median: 1.6 mGy; range: ~0 mGy to 0.38 Gy) due to inhalation of short-lived radionuclides. Internal exposure of the thyroid gland to ^{131}I contributed more than 50% of the total thyroid dose in 45% of the study subjects. The uncertainties in the individual stochastic doses were characterized by a mean geometric standard deviation of 2.0, 1.8, 2.0, and 2.6 for external irradiation, inhalation of ^{131}I, inhalation of short-lived radionuclides, and residential exposure, respectively. The models used for dose calculations were validated against instrument measurements done shortly after the accident. Results of the validation showed that thyroid doses could be estimated retrospectively for Chernobyl cleanup workers two to three decades after the accident with a reasonable degree of reliability.**
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Key words: Chernobyl, cleanup worker, thyroid, radiation, dose

INTRODUCTION

THE ACCIDENT at the Chernobyl (Chornobyl) nuclear power plant (NPP) occurred on 26 April 1986 and resulted in heavy radioactive contamination of buildings and ground surface at the Chernobyl site and within the surrounding 30 km zone. Several hundred thousand workers, called cleanup workers or liquidators, participated in decontamination and recovery activities within the 30 km zone until the end of 1990. Approximately 306,000 of these (the majority from Ukraine, Russian Federation, and Belarus) worked in 1986 when the highest doses were received (UNSCEAR 2011). The main cleanup workers' activities included decontamination of the reactor block and reactor site, construction of the sarcophagus (Object Shelter) and living quarters for the Chernobyl NPP personnel, working at the waste repositories, and safeguarding the 30 km zone and evacuated settlements.

A majority of cleanup workers were exposed to external radiation (Chumak 2007; Kryuchkov et al. 2009, 2012). However, those who were involved in cleanup activities during the first 10 d after the accident may have received radiation doses to the thyroid gland resulting primarily from inhalation of air contaminated with ^{131}I (Drozdovitch et al. 2019). Epidemiological studies of Chernobyl cleanup workers (Furukawa et al. 2012; Kesminiene et al. 2012) suggested that internal exposure of adults to ^{131}I may cause an increased risk of radiation-related thyroid cancer. Mabuchi et al. (2013) argued that there is a need for better understanding of radiation-related thyroid cancer risk following exposure in adulthood.

To fill this gap in knowledge, a case-control study of thyroid cancer nested in a cohort of Ukrainian cleanup workers was conducted in 2009–2017 by the National Research Center for Radiation Medicine (Kyiv [Kiev], Ukraine)

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The authors declare no conflicts of interest.

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and the US National Cancer Institute (Bethesda, MD). In the current study, methods were developed to reconstruct individual thyroid doses to support the epidemiological study of Chernobyl cleanup workers.

MATERIALS AND METHODS

Study population

A nested case-control study of thyroid cancer was conducted in the cohort of 150,813 male adult Ukrainian liquidators who worked at the industrial site and in the most contaminated areas around the Chernobyl nuclear power plant between 26 April 1986 and 31 December 1990. The thyroid cancer cases were ascertained retrospectively through the linkage of the cohort of male Ukrainian cleanup workers with the Ukrainian Cancer Registry in five study oblasts[5] (Kyiv, Chernihiv, Dnepropetrovsk, Donetsk, and Kharkiv), and in Kyiv city during the postaccident period until 2012. For each case ($n = 149$), at least three controls were matched by year of birth (±2 y), oblast of residence, and living at the time of diagnosis of the case.

Cleanup workers were involved in various cleanup activities, worked under different radiation monitoring and safety conditions, and were ultimately exposed to different types and levels of radiation. Major categories of cleanup workers, who were the subjects of this study, included military (236 individuals, 38.9% of the total); civilians who performed various tasks in the 30 km zone, so-called "sent on mission" (137 individuals, 22.6%); early cleanup workers (64 individuals, 10.5%); and a mixed category that includes cleanup workers who were at the Chernobyl site a few times as members of different categories (152 individuals, 25.0%).

A special dosimetry questionnaire was designed to collect retrospective information to be used for dose reconstruction, including items about locations, dates, and conditions of cleanup workers' activities as well as place of residence during the cleanup mission. The questionnaire was a modified version of the instrument successfully used in the Ukrainian-American study of leukemia and related disorders (Chumak et al. 2008). Modifications included additional questions about dates of intake of potassium iodine (KI) pills for iodine prophylaxis during cleanup mission and about the subject's residential history and diet during residence in contaminated settlements (see section on thyroid dose due to ^{131}I intake not related to the work as a Chernobyl liquidator). The questionnaire also contained supplementary epidemiological data needed for the consequent risk analysis (to account for confounding factors), such as anthropometry, professional and/or medical contacts with ionizing radiation, family history of thyroid cancer, smoking/alcohol consumption habits, etc. The current questionnaire was administered in interviews with the study subjects carried out by trained personnel during the period of 15 November 2010–5 May 2016, some 25–30 y after the accident. In the case of deceased or incapable subjects, two proxies were interviewed: (1) the next of kin, usually the spouse, who provided supplementary epidemiological data and the names of persons who worked together with the subject at Chernobyl site, and (2) identified colleague(s) who described the cleanup activities of the subject. The interviewer also collected and copied additional relevant information from the interviewee: certificates, itineraries of the cleanup worker's transportation, etc.

Radiation dose reconstruction

Liquidators who worked at the Chernobyl NPP site and in the 30 km zone were exposed to external radiation from radionuclide-contaminated buildings and soil surface. Those who started their mission during the first 10 d after the accident may have received radiation doses to the thyroid due to inhalation of ^{131}I in contaminated air. Inhalation of short-lived radioiodines and radiotelluriums could also contribute to exposure of the thyroid gland, and therefore, this source of internal exposure was also considered in the study. In addition to the dose received as a cleanup worker, the dose received in the places of residence could also be a substantial component of thyroid exposure. Cleanup workers who resided in the highly contaminated northern part of Ukraine might have received thyroid doses at their places of residence due to consumption of locally produced food contaminated with ^{131}I. Table 1 summarizes characteristics of components of thyroid dose that were reconstructed for the study.

The way individual thyroid doses due to different exposure pathways were estimated to the study subjects is described in the following sections.

Thyroid doses due to external irradiation related to the cleanup worker mission

To estimate external doses to cleanup workers, a time-and-motion method named Realistic Analytical Dose Reconstruction With Uncertainty Estimation (RADRUE) was used (Kryuchkov et al. 2009). The RADRUE technique calculates external dose as a product of the exposure rate and time of irradiation accounting for shielding properties of the local environment (location factor). The external dose absorbed in the thyroid gland during a cleanup worker mission resulted from the summation of the products of

[5] An oblast is the largest administrative unit in Ukraine. The typical size of an oblast is 20,000–30,000 km^2 with a population of 1.1–4.3 million persons.

Table 1. Characteristics of components of thyroid doses that were reconstructed for the study subjects.

Component	Pathway of exposure	Time frame of exposure	Exposure occurred at
External	Gamma-emitting radionuclides	Cleanup mission between 26 April 1986 and 31 December 1990	Chernobyl NPP and within the 30 km zone
Internal	Inhalation of ^{131}I	Cleanup mission between 26 April 1986 and 6 May 1986	Chernobyl NPP and within the 30 km zone
Internal	Inhalation of ^{132}I, ^{133}I, ^{135}I, ^{131m}Te, and ^{132}Te	Cleanup mission between 26 April 1986 and 6 May 1986	Chernobyl NPP and within the 30 km zone
Internal	Intake of ^{131}I via inhalation and in locally produced food	Residence between 26 April 1986 and 30 June 1986	Settlement of residence

exposure rate, duration, and location factor during each time interval of exposure to radiation:

$$D_{\text{ext}} = \sum_{i=1}^{N_i} \sum_{j=1}^{N_j} C_{\text{th}} \times P\left[x(t_j), y(t_y)\right] \times \Delta t_j \times L_j, \qquad (1)$$

where D_{ext} is the thyroid dose due to external irradiation for the study subject (mGy); N_i is the number of days in cleanup mission of the study subject; N_j is the number of cleanup activities at different locations on day i considered in the calculation (usually unequal between different days of cleanup mission). Activities included time spent working, traveling, or resting during the cleanup mission; C_{th} is the conversion coefficient from ambient dose rate in air to the absorbed dose in the thyroid (mGy h^{-1} per mGy h^{-1}); $P[x(t_j),y(t_j)]$ is the ambient dose rate in air (mGy h^{-1}) at the location $[x(t_j),y(t_j)]$ and at time t_j, where and when the study subject was present; Δt_j is the time interval of performing of complete cleanup activity j by the study subject (h); L_j is the location factor at the location of the cleanup activity j (unitless).

It should be noted that the computer code initially developed to implement the RADRUE method was modified for the purposes of this study to a new computer code named Rockville. Algorithms to calculate organ-specific doses due to external irradiation used in the code RADRUE were completely transferred to the code Rockville and validated by an international group of dosimetry experts. The major modifications were the following:

- Development of a special module to calculate thyroid doses due to inhalation of ^{131}I and short-lived radioiodine and radiotellurium isotopes.
- Creation of regular grids of radiation data (exposure rate in air, ^{131}I concentration in air, etc.) using different geostatistical interpolation techniques. Fig. 1 shows gridlines of exposure rates in air that are implemented

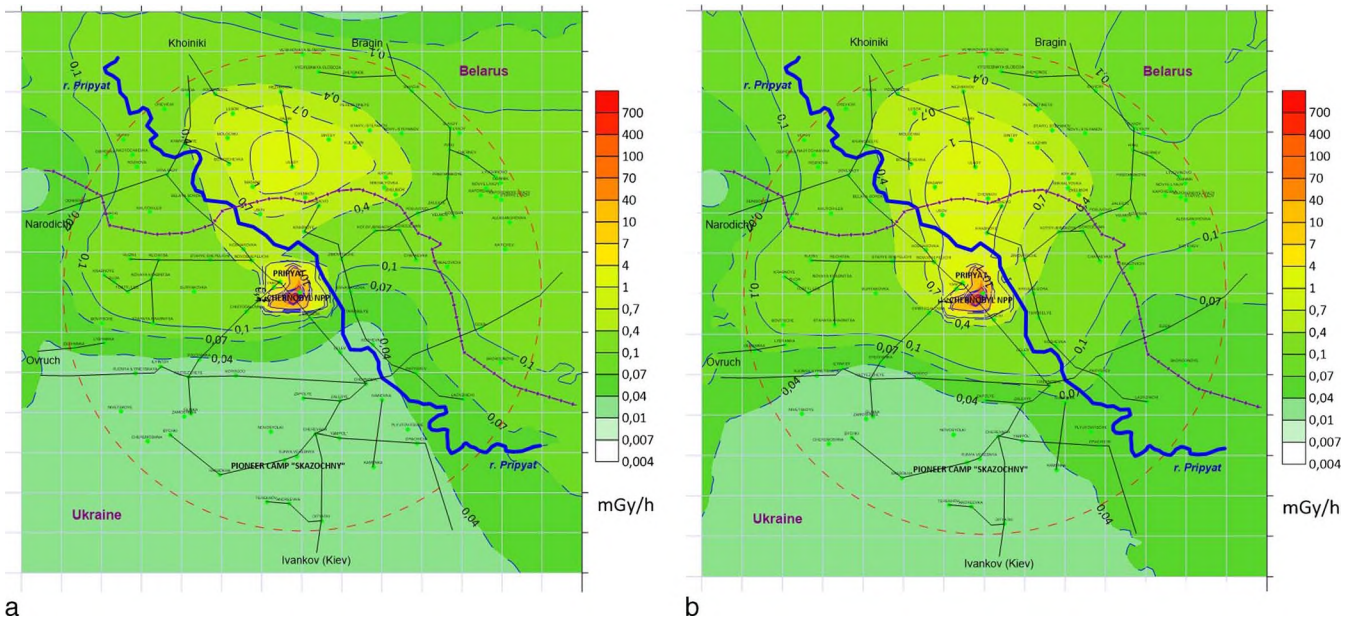

Fig. 1. Grids of ambient dose rate in air in the 30 km zone around the Chernobyl NPP: on (a) 26–27 April 1986 and (b) 28–29 April 1986. Point with coordinates (0, 0) is the 4th unit of the Chernobyl NPP.

in computer code Rockville for the 30 km zone around the Chernobyl NPP, as an example, on 26–27 April and 28–29 April 1986.
- Improvement of databases of the site and buildings of Chernobyl NPP.
- Improvement of the algorithm to calculate radiation doses inside buildings of Chernobyl NPP.
- Visualization of the radiation situation to facilitate questionnaire data entry for a dosimetry expert and the possibility of using Google Maps (Google, Inc., Mountain View, California, US) and Microsoft Virtual Earth (Microsoft Corp., Redmond, Washington, US) with different scales.

Doses calculated using the RADRUE method were compared to the most reliable measured doses available for different groups of cleanup workers. It was shown that RADRUE doses agreed reasonably well within the uncertainty range with measured doses. Detailed descriptions of questionnaire data processing, entering, and validation that are applied in the RADRUE method and of validation exercises for the RADRUE method can be found elsewhere (Kryuchkov et al. 2009).

Thyroid doses due to ^{131}I inhalation during the cleanup worker mission

To calculate the individual thyroid doses to Chernobyl cleanup workers from ^{131}I inhalation, the model developed by Drozdovitch et al. (2019) was used. It considers the following factors: the ground-level outdoor air concentrations of ^{131}I at the locations where the liquidator worked and resided, the reduction of ^{131}I activity in inhaled air due to indoor occupancy, the time spent indoors by the cleanup worker, the breathing rate during different physical activities, and intake of KI pills for iodine prophylaxis.

As was mentioned above, a special module was designed for computer code Rockville to calculate thyroid dose due to ^{131}I inhalation. Similar to calculation of thyroid dose due to external irradiation, information on whereabouts (location, duration, indoors/outdoors) and activities performed by the study subjects was used to calculate thyroid dose due to ^{131}I inhalation using the following equation:

$$D_{\text{inh}}^{\text{I-131}} = \frac{13.82 \times E_{\text{th}}}{m_{\text{th}}} \times \sum_{i=1}^{N} \left[\left[\sum_{j=1}^{N_j} I_{\text{inh},j} \times w_{\text{inh}} \times w_{\text{th}} \times CF_{\text{KI},i} \right] + Q_{\text{thyr,inh},i\text{-}1} \times e^{-\left(\lambda_{\text{th}} + \lambda_{\text{r,I-131}}\right)} \right], \quad (2)$$

where $D_{\text{inh}}^{\text{I-131}}$ is the thyroid dose due to inhalation of ^{131}I for the study subject (mGy); 13.82 is a unit conversion factor (Bq kBq^{-1} g kg^{-1} J MeV^{-1} s d^{-1} mGy Gy^{-1}); E_{th} = 0.2 MeV is the mean energy absorbed in the thyroid per decay of ^{131}I in the thyroid; m_{th} is the thyroid mass for adult male (g); N = 66 is the number of days counted since the accident until complete elimination of ^{131}I from the thyroid after inhalation; $I_{\text{inh},j}$ is the intake function of ^{131}I with contaminated air at the location of the cleanup activity j during the day i (kBq); w_{inh} is the fraction of inhaled iodine transferred to blood (unitless); w_{th} is the fraction of iodine uptake by the thyroid (unitless); $CF_{\text{KI},i}$ is the correction factor on day i of w_{th} that varies with time after intake of stable iodine for prophylactic reason (Table A1.4 from Drozdovitch et al. 2013) (unitless); $Q_{\text{thyr,inh},i\text{-}1}$ is the activity in the thyroid of the study subject on day $i-1$ due to inhalation of ^{131}I (kBq); $\lambda_{\text{th}} = \text{LN}(2)/T_{\text{b}}$ is the rate of biological elimination of iodine from the thyroid (d^{-1}); T_{b} is the biological half-time of iodine removal from the thyroid (d); $\lambda_{\text{r,I-131}} = 0.0862$ d^{-1} is the radioactive decay rate of ^{131}I.

Values of dosimetry model parameters are given below in the section on uncertainties in thyroid doses. The intake function of ^{131}I with contaminated air was calculated as:

$$I_{\text{inh},j} = C_{\text{air},i,j}^{\text{I-131}} \times B_{m,j} \times \Delta t_j \times F_j, \quad (3)$$

where $C_{\text{air},i,j}^{\text{I-131}}$ is the time-integrated activity of ^{131}I in air at the location of the j-th cleanup activity during the day i (kBq d m^{-3}); B_{mj} is the breathing rate for an adult person according to the International Commission on Radiological Protection report (ICRP 2002) that correspond to the physical activity m of the subject at the location of the cleanup activity j (m^3 d^{-1}); Δt_j is the time interval of performing cleanup activity j by the study subject (d); F_j is the reduction factor of ^{131}I activity in air that is associated with indoor occupancy at the location of the j-th cleanup activity (unitless). F_j = 0.1, 0.3, and 0.5 if the study subject stayed indoors in Pripyat Town, buildings of the Chernobyl NPP, or a rural settlement in the 30 km zone around the Chernobyl NPP, respectively, and F_j = 1 if the study subject stayed outdoors.

Values of average daily ^{131}I concentration in ground-level air were calculated for each settlement in Ukraine using the atmospheric transport model developed by Talerko (2005a and b). Fig. 2 shows implemented computer code Rockville gridlines of ^{131}I concentration in air in the 30 km zone around the Chernobyl NPP, as an example, on 26 April and 27 April 1986.

Validation of model. This model was validated by a data set of measurements of exposure rate near the neck, called direct thyroid measurements, performed from 30 April to 5 May 1986 in a group of 594 cleanup workers. Although the study subjects in this group of measured cleanup workers were not identified, the ^{131}I activities in the thyroids, which were calculated using the model, were compared with those estimated from the direct thyroid

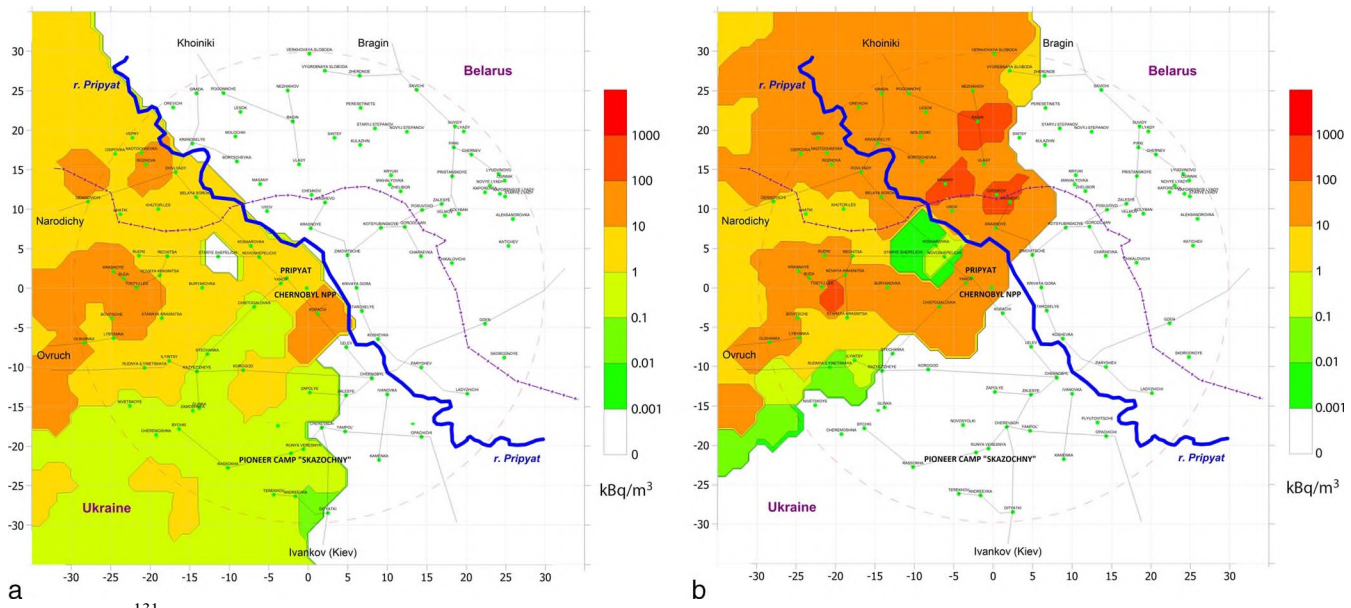

Fig. 2. Daily ^{131}I concentration in air in the 30 km zone around the Chernobyl NPP on (a) 26 April 1986 and (b) 27 April 1986. Point with coordinates (0, 0) is the 4th unit of the Chernobyl NPP.

measurements done for 594 cleanup workers. The arithmetic mean ± standard deviation of the ratios of measured-to-calculated activities of ^{131}I in the thyroid was found to be 1.6 ± 2.4 (median was 0.8). Among this group of measured cleanup workers, detailed descriptions of hour-by-hour whereabouts and work history were available for 60 individuals. For these cleanup workers the mean of the ratios of measured-to-calculated activities was found to be 1.2 ± 0.7 (median was 1.0). Fig. 3 compares thyroid doses due to ^{131}I inhalation calculated by the model with those derived from direct thyroid measurements for 60 cleanup workers with detailed work history. As can be seen from the figure, the two sets of doses agree for 92.6% of individuals within a factor of 3 (shown by broken lines); the coefficient of correlation is $r = 0.75$. Detailed descriptions of the model validation can be found elsewhere (Drozdovitch et al. 2019).

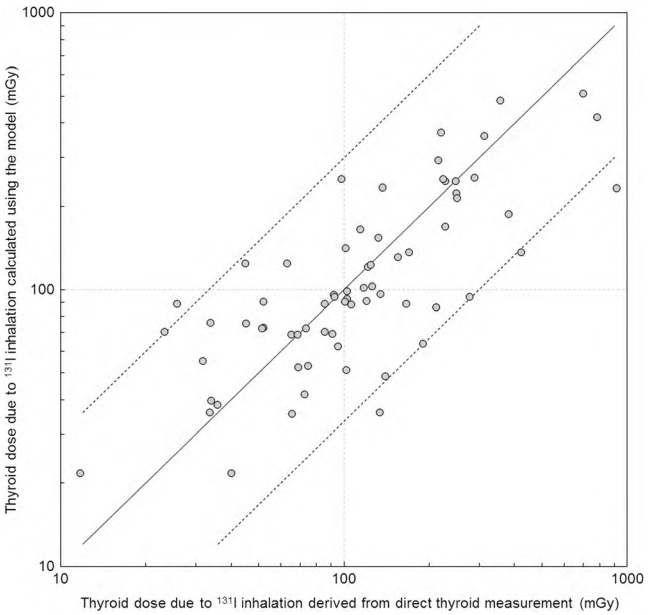

Fig. 3. Comparison of thyroid doses due to ^{131}I inhalation calculated by the model with those derived from direct thyroid measurements. Broken lines show factor of 3 difference between two sets of doses.

Results of the model validation indicated that thyroid dose due to ^{131}I inhalation could be estimated for Chernobyl cleanup workers with a reasonable degree of reliability. However, because direct thyroid measurements were not available for the study subjects, dose estimation requires detailed information on whereabouts and work history of the cleanup worker collected in this case-control study for all subjects by means of personal interview. Unfortunately, it was not possible to evaluate the reliability of the interview responses provided by the study subjects or proxies as there are no gold standard data (e.g., historical questionnaires obtained shortly after the cleanup mission) for them to compare with.

Thyroid doses due to inhalation of short-lived radioiodine and radiotellurium isotopes during the cleanup worker mission

A nuclear reactor produces several short-lived radioiodine isotopes with the same behavior in the environment and the human body as ^{131}I. Also, the radiotellurium isotopes, which are the precursors of the radioiodines, need to be taken into consideration. Because of the short half-time of these radionuclides, inhalation of only ^{132}I, ^{133}I, ^{135}I, ^{131m}Te, and ^{132}Te contributed to the thyroid exposure

(Balonov et al. 2003). Thyroid dose due to inhalation of short-lived radioiodine and radiotellurium isotopes was estimated as a fraction of thyroid dose due to inhalation of ^{131}I using the approach suggested by Gavrilin et al. (2004):

$$D^{m}_{\mathrm{inh},i} = D^{\mathrm{I-131}}_{\mathrm{inh},i} \times R_{\mathrm{dose},m,i}, \quad (4)$$

where $D^{m}_{\mathrm{inh},i}$ is the thyroid dose due to inhalation of short-lived radionuclide m for the study subject on day i (mGy); $R_{\mathrm{dose},m,i}$ is the ratio of thyroid doses due to inhalation of short-lived radionuclide m to that of ^{131}I on day i (unitless).

The ratio for each day from 26 April through 6 May, when inhalation of ^{131}I and short-lived radionuclides occurred, can be expressed as:

$$R_{\mathrm{dose},m,i} = \frac{D^{m}_{\mathrm{inh},i}}{D^{\mathrm{I-131}}_{\mathrm{inh},i}} = R_{\mathrm{DF},m} \times R_{\mathrm{air},m,i}, \quad (5)$$

where $R_{\mathrm{DF},m,i}$ is the ratio of the inhalation thyroid dose coefficients of radionuclide m to that of ^{131}I on day i (ICRP 1995) (unitless); $R_{\mathrm{air},m,i}$ is the ratio of the intakes due to inhalation of radionuclide m to that of ^{131}I on day i that is equal to the ratio of average concentration in ground-level air of radionuclide m to that of ^{131}I on day i (unitless).

Values of $R_{\mathrm{air},m,i}$ were calculated using the following equation:

$$R_{\mathrm{air},m,i} = R_{\mathrm{air},m,0} \times \mathrm{e}^{-\lambda_{\mathrm{r},m} \times t} \quad (6)$$

where $R_{\mathrm{air},m,0}$ is the ratio of the activity of radionuclide m to ^{131}I in the reactor core at the time of the explosion (unitless) (Gavrilin et al. 2004); $\lambda_{\mathrm{r},m}$ is the radioactive decay rate of radionuclide m (d^{-1}); t is the time after the accident (d).

Table 2. Parameters of model and results of calculation of the ratios of thyroid dose due to inhalation of short-lived radionuclides to thyroid dose due to ^{131}I inhalation.

	^{131m}Te	^{132}Te	^{132}I[a]	^{133}I	^{135}I	Total
$R_{\mathrm{DF},m}$	0.082	0.17	0.009	0.19	0.038	—
$R_{\mathrm{air},m,0}$	0.18	1.30	1.33	1.48	0.91	—
$\lambda_{\mathrm{r},m}$ (d^{-1})	0.555	0.213	7.23	0.8	2.52	—
$R_{\mathrm{dose},m,i}$						$R_{\mathrm{dose},i}$
26 April	0.012	0.208	0.012	0.202	0.013	0.447
27 April	0.007	0.183	0.010	0.099	0.001	0.300
28 April	0.005	0.161	0.009	0.048	—	0.223
29 April	0.003	0.142	0.008	0.024	—	0.177
30 April	0.002	0.125	0.007	0.012	—	0.146
1 May	0.001	0.110	0.006	0.006	—	0.123
2 May	0.001	0.097	0.005	0.003	—	0.106
3 May	—	0.085	0.005	0.001	—	0.091
4 May	—	0.075	0.004	0.001	—	0.080
5 May	—	0.066	0.004	—	—	0.070
6 May	—	0.058	0.003	—	—	0.061

[a]Result of calculation is given for radioactive equilibrium with precursor ^{132}Te.

Table 3. Distribution of the study subjects according to the place of residence at the time of the accident and range of ^{137}Cs and ^{131}I deposition in locations of residence.

		Deposition density (kBq m^{-2})	
Place of residence	N	^{137}Cs	^{131}I
Kyiv Oblast	222	6.3–4,640	115–536,600
Kyiv City	136	26	470
Chernihiv Oblast	37	2.1–64	33–1,055
Dnipropetrovsk Oblast	95	1.1–15	7.0–95
Donets'k Oblast	54	3.3–38	15–205
Kharkiv Oblast	21	5.8–15	32–83
Zhytomir Oblast	8	4.4–375	67–6,335
Other oblasts of Ukraine	16	1.6–18	14–250
Outside Ukraine	18	0–18,530	0–507,400
Entire study	607	0–18,530	0–536,600

Values of parameters of the model to calculate the ratios of thyroid dose due to inhalation of short-lived radionuclides to thyroid dose due to inhalation of ^{131}I and results of the calculation are given in Table 2. As can be seen from the table, by the end of the inhalation intake on 6 May 1986, the thyroid dose was almost entirely defined by ^{131}I.

Thyroid dose due to ^{131}I intake not related to the work as a Chernobyl liquidator (residential exposure)

Due to the wide-spread contamination of the Ukrainian territory following the Chernobyl accident, cleanup workers from Ukraine additionally received radiation doses to the thyroid due to ^{131}I intake from locally produced food while residing in contaminated settlements between 26 April and 30 June 1986. Some study subjects spent some time in the southeastern part of Belarus that was also highly contaminated with ^{131}I. The distribution of study subjects according to the oblast of residence at the time of the accident and the range of ^{137}Cs and ^{131}I deposition in the settlements of residence is given in Table 3.

Values of ^{131}I ground deposition were calculated by Talerko (2005a and b) using the atmospheric transport model developed for Ukraine. Fig. 4 shows ^{131}I ground deposition in the study oblasts that was accumulated from 26 April through 6 May 1986.

To estimate the radiation doses due to ^{131}I intakes not related to the work as a Chernobyl cleanup worker, the study dosimetry questionnaire was extended with a section designed to elicit information on the subject's residential history; consumptions of locally produced cow's milk, milk products, and leafy vegetables; and administration of stable iodine to blockade intake of radioiodine. In the case of a deceased or incapable subject, the spouse was interviewed to provide this information.

Direct thyroid measurements that were done shortly after the accident are the best basis for estimating reliable instrumental thyroid doses due to ^{131}I intake. Unfortunately,

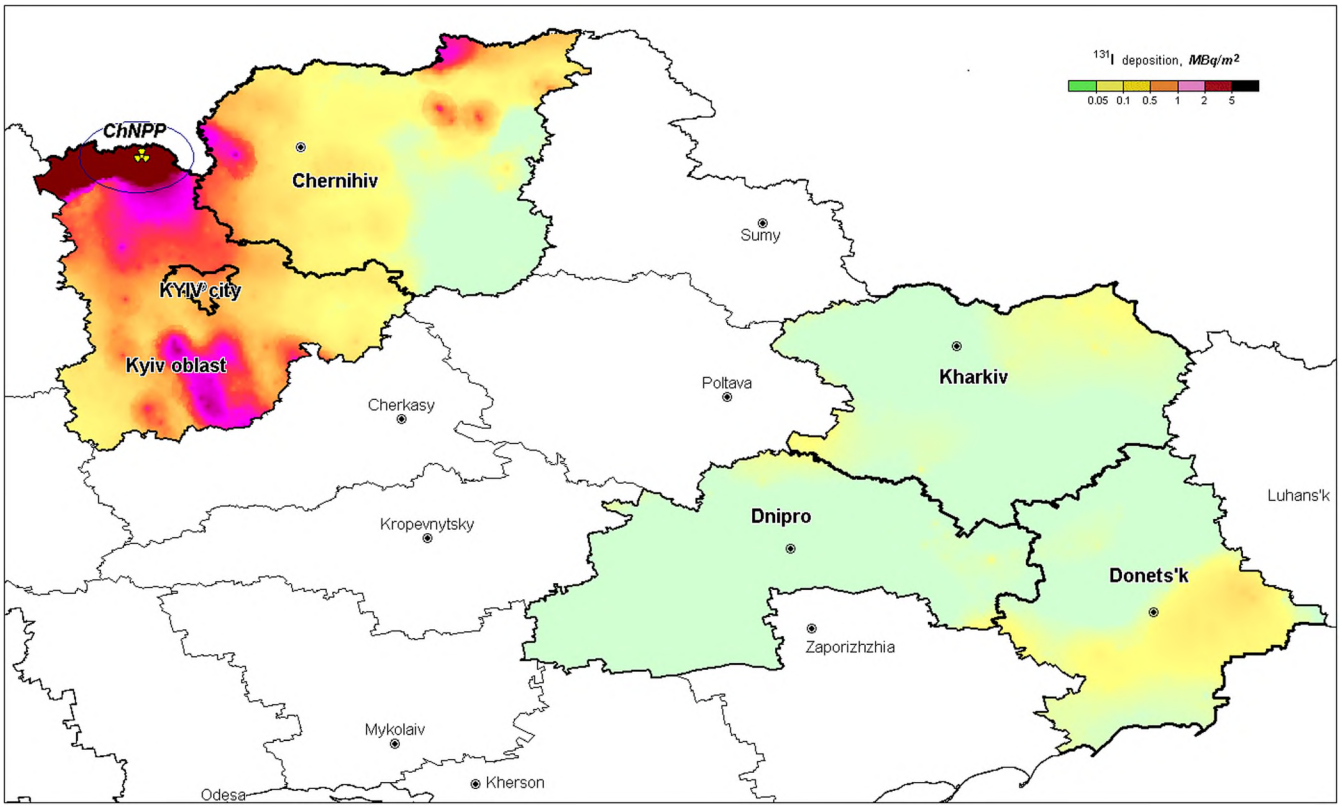

Fig. 4. ^{131}I ground deposition in the study oblasts that accumulated from 26 April through 6 May 1986.

no overlap was found in the course of the linkage of the list of 607 study subjects with the database of around 50,000 direct thyroid measurements done in Ukraine among adults (Likhtarov et al. 2005). Therefore, only dose based on an ecological model can be calculated for the subjects included in this study. Information obtained during the personal interviews was input into an ecological model that describes transport of ^{131}I from the environment to milk and dairy products and, finally, to the human body and thyroid. Time-integrated ^{131}I activity in the thyroid, estimated via the ecological model, determined the ecological dose. The ecological model, which was used to calculate the thyroid dose due to ^{131}I intakes during residence, is described in detail by Drozdovitch et al. (2013) with adaption to region-specific parameters for Ukraine (Likhtarov et al. 2014).

In brief, ecological thyroid dose due to ^{131}I intake during residence of the study subject was calculated using the following equation:

$$D_{\mathrm{ecol,res}}^{\mathrm{I-131}} = \frac{13.82 \times E_{\mathrm{th}}}{m_{\mathrm{th}}} \times \sum_{k=1}^{N} \left[I_{\mathrm{ing},k} \times w_{\mathrm{ing}} \times w_{\mathrm{th}} \times CF_{\mathrm{KI},k} + Q_{\mathrm{thyr,ing},k-1} \times \mathrm{e}^{-\left(\lambda_{\mathrm{th}} + \lambda_{\mathrm{r,I-131}}\right)} \right], \quad (7)$$

where $D_{\mathrm{ecol,res}}^{\mathrm{I-131}}$ is the ecological thyroid dose due to ^{131}I intake with locally produced foodstuffs during residence for the study subject (mGy); $N = 66$ is the number of days counted from the accident until complete elimination of ^{131}I from the thyroid after ^{131}I intake during residence until 30 June 1986; $I_{\mathrm{ing},k}$ is the intake function of ^{131}I in foodstuffs during day k (kBq); $w_{\mathrm{ing}} = 1.0$ is the fraction of ingested iodine transferred to blood (ICRP 1993) (unitless); $Q_{\mathrm{thyr,ing},k\text{-}1}$ is the activity in the thyroid of the study subject on day $k-1$ due to ingestion of ^{131}I (kBq).

The intake function of ^{131}I with foodstuffs was calculated as:

$$I_{\mathrm{ing},k} = \sum_{n} C_{n,k} \times \mathrm{e}^{-\lambda_{\mathrm{r,I-131}} \times \Delta t_n} \times RF_n \times V_{n,k}, \quad (8)$$

where $C_{n,k}$ is the activity of ^{131}I in foodstuff n consumed by the study subject at the settlement of residence on day k (kBq L^{-1}[kg^{-1}]); Δt_n is the time lag between production and consumption of foodstuff n (d); RF_n is the reduction factor of ^{131}I activity in foodstuff n in comparison with raw foodstuff due to culinary processing (unitless); $V_{n,k}$ is the consumption rate of foodstuff n by the study subject on day k reported during the personal interview (L [or kg] d^{-1}).

Consumption of the following foodstuffs was important for ^{131}I intake:

- Milk from privately owned cows as is common in rural settlements.
- Cow's milk from the commercial trade network that is common in urban settlements.

- Sour milk and/or kefir.
- Sour cream and/or soft cottage cheese.
- Leafy green vegetables.

Activity concentration of ^{131}I in milk from privately owned cows produced at the settlement of residence was calculated as:

$$C_{\text{privmilk}}(t) = TF_m \times \int_{t_1}^{t_2} A_c(\tau) \times \lambda_b \times e^{-(\lambda_b + \lambda_{r,I-131}) \times (t-\tau)} d\tau, \quad (9)$$

where TF_m is the feed to cow's milk transfer factor of ^{131}I (d L^{-1}); $A_c(\tau)$ is the daily ^{131}I activity intake by cows (kBq d^{-1}); λ_b is the rate of biological elimination of ^{131}I from cow's milk (d^{-1}); t_1 and t_2 are time of arrival and departure from the settlement of residence counted from the time of the accident (d).

The main sources of ^{131}I intake by cows were consumption of pasture grass and, because of the low stage of grass development in early spring shortly after the accident, ingestion of soil on pasture. Therefore, the daily ^{131}I activity intake by cows was calculated as:

$$A_c(t) = GD_{I-131}(0) \times \left[\frac{f}{Y_{gr}} \times I_{gr} \times e^{-\lambda_{gr} \times t} + \frac{1-f}{Y_{soil}} \times I_{soil} \times e^{-\lambda_{r,I-131} \times t} \right], \quad (10)$$

where GD_{I-131} is the ground deposition of ^{131}I at the settlement of residence at the time of deposition (kBq m^{-2}); f is the interception coefficient of ^{131}I by grass (unitless); I_{gr} and I_{soil} are the daily consumption of grass and soil by cows, respectively (kg d^{-1}); Y_{gr} is the pasture grass yield (kg m^{-2}); λ_{gr} is the removal rate of ^{131}I from grass (d^{-1}); Y_{soil} is the mass of the top layer of soil per unit of ground (kg m^{-2}); t is the time after deposition (d).

Activity of ^{131}I in leafy green vegetables was calculated as:

$$C_{LV}(t) = \frac{GD_{I-131}(0) \times f}{Y_{gr}} \times e^{-\lambda_{gr} \times t}. \quad (11)$$

However, as was shown in persons with direct thyroid measurements, there is an area-specific bias between ^{131}I thyroidal activities calculated using the ecological model and those derived from direct thyroid measurements (Drozdovitch et al. 2013; Likhtarov et al. 2014). Therefore, to provide more realistic and reliable estimates of thyroid doses due to ^{131}I intake during residence, ecological thyroid doses calculated for the study subjects were adjusted in the following way:

$$D_{res}^{I-131} = \sum_{l=1}^{N} RA_l \times \frac{D_{ecol,res,l}^{I-131}}{SF_l}, \quad (12)$$

where D_{res}^{I-131} is the adjusted thyroid dose due to ^{131}I intake during residence (mGy); RA_l is the type of settlement-specific relative time-integrated activity of ^{131}I in the thyroid (unitless); $D_{ecol,res,l}^{I-131}$ is the ecological thyroid dose due to ^{131}I intake during residence at settlement l (mGy); and SF_l is the scaling factor used to adjust ecological thyroid dose due to ^{131}I intake during residence at settlement l (unitless).

The scaling factor used to adjust ecological thyroid dose due to ^{131}I intake for a given individual was derived from comparison of ^{131}I activities in the thyroid estimated from direct thyroid measurement and calculated using the ecological model for the time of measurement. As was mentioned above, direct thyroid measurements did not occur for the subjects included in this study. To adjust ecological dose, the following approach developed by Likhtarov et al. (2005) for two groups of individuals without direct thyroid measurements was used:

1. The study subjects resided in areas (raions) where direct thyroid measurements were done in May–June of 1986. For these subjects, a raion-specific scaling factor derived from direct thyroid measurements of other male individuals was used to adjust ecological thyroid dose (Table 4).
2. The study subjects resided in raions where no direct thyroid measurements were done. For these subjects, a scaling factor was calculated for the settlement of residence using the following purely empirical equation:

$$SF_l = B \times \left(GD_{Cs-137,l}\right)^{\beta}, \quad (13)$$

where $GD_{Cs-137,l}$ is the ^{137}Cs ground deposition in settlement l (kBq m^{-2}); B and β are parameters of the fitting function.

Values of dosimetry model parameters are given in the section on uncertainties in thyroid doses. It should be noted that thyroid dose due to inhalation of ^{131}I during residence was calculated using the same approach as for the cleanup mission using eqns (2) and (3).

Table 4. Raion-specific values of scaling factor (Likhtarov et al. 2005).

Oblast	Raion	Raion-specific values of scaling factor SF_l[a]			
		AM	SD	GM	GSD
Zhytomir	Korosten	6.2	3.4	5.4	1.7
Zhytomir	Narodychi	2.8	2.3	2.2	2.1
Zhytomir	Ovruch	3.9	2.6	3.2	1.8
Kyiv	Borodianka	6.9	4.8	5.7	1.9
Kyiv	Vyshhorod	4.8	2.3	4.3	1.6
Kyiv	Ivankiv	6.0	4.3	4.9	1.9
Kyiv	Makariv	2.1	1.1	1.9	1.6
Kyiv	Poliske	10.5	17.7	5.4	3.2
Chernihiv	Kozelets	2.5	1.9	2.0	2.0
Chernihiv	Ripky	2.3	4.4	1.1	3.5
Chernihiv	Chernihiv	1.3	1.8	0.8	2.8

[a]AM: arithmetic mean; SD: standard deviation; GM: geometric mean; GSD: geometric standard deviation.

Uncertainties in thyroid doses

Monte Carlo simulation was used to estimate the uncertainties in thyroid doses received by the study subjects. A set of multiple (typically 1,000 or 10,000) individual stochastic doses (trials) was calculated for each study subject (if only unshared errors were considered) or for the entire study population (if shared and unshared errors were considered).

Thyroid doses calculated using RADRUE method: external irradiation and inhalation of ^{131}I and short-lived radionuclides during the cleanup mission. The RADRUE method allows us to estimate the dose and the uncertainties in the dose estimates associated with uncertainties in the input parameters. The same information on location of cleanup mission, its duration, staying indoors/outdoors, and activities performed by the study subjects are used in computer code Rockville for calculation of thyroid dose due to external irradiation and inhalation of ^{131}I and short-lived radionuclides. Therefore, these three exposure pathways are considered here together.

Parameters of the RADRUE model and their distributions used to calculate individual stochastic thyroid doses are given in Table 5. All parameters were considered to be sources of unshared errors. A separate study was conducted to evaluate the significance of accounting for sources of shared and unshared errors in the estimation of uncertainties in the RADRUE doses. Kryuchkov et al. (2009) evaluated the probability that two or more cleanup workers, from the 434 who were on mission in 1986, were at the same location at the same time and therefore, the probability that their doses were defined by the exposure rate (or ^{131}I concentration in air) shared at that location. The result of the study shows that the shared dose caused by the situation when individuals shared the same location at the same time represents less than 1% of the total dose.

Thyroid dose due to ^{131}I intake during residence. An approach similar to that used in the studies of thyroid cancer and other thyroid diseases in Belarusian-American (BelAm) and Ukrainian-American (UkrAm) cohorts (Drozdovitch et al. 2015; Likhtarov et al. 2014) was used here to estimate uncertainties for the thyroid dose due to ^{131}I intake during residence. According to this approach, 1,000 sets of the study population thyroid doses, considering sources of shared and unshared errors, were calculated. For a specific dose realization, some of the model parameter values were considered to be shared (common) among the study subjects who represented the entire study population or specific subgroups. These subject-independent (or shared) parameters included parameters of the ecological model describing variation with time of ^{131}I contamination in the ground and foodstuff (Table 6). Other sources of errors were considered to be subject dependent (or unshared). This group of errors included errors in assigning a thyroid mass value to the study subject, parameters of biokinetic models of iodine in the human body (Tables 5 and 7), and uncertainties associated with the imprecise answers on relocation history and individual consumption reported during personal interviews (Tables 8 and 9).

For the implementation of this approach, values for shared parameters were assigned before the calculation of each dose set for the entire study population. The same value for each shared parameter was used to calculate one dose set for all study subjects for whom this parameter was assigned to be shared. During the calculation of dose sets, values of unshared parameters were sampled from their distributions for each study subject, and one dose set was calculated for the entire study population. The 1,000 realizations of dose for a given study subject represent the individual stochastic thyroid doses assigned to this person.

RESULTS

Individual thyroid doses

Table 10 provides a summary of thyroid doses reconstructed for study subjects from different exposure pathways. The arithmetic mean of thyroid doses among the study subjects was estimated to be 199 mGy, including 140 mGy from external irradiation during the cleanup mission, 44 mGy due to ^{131}I inhalation, 11 mGy due to inhalation of short-lived radionuclides, and 42 mGy due to ^{131}I intake during residence. It should be noted that arithmetic means of thyroid doses are given only for the study subjects who were exposed to the given exposure pathway. Therefore, the arithmetic mean of the total dose is not equal to the sum of arithmetic means of components of the dose. The median thyroid dose from all exposure pathways was estimated to be 47 mGy. Individual thyroid doses from external exposure ranged up to 3,630 mGy; from ^{131}I inhalation, up to 1,680 mGy; from inhalation of short-lived radionuclides, up to 377 mGy; and from exposure to ^{131}I during residence, up to 3,430 mGy. The maximal individual thyroid dose from all exposure pathways was found to be 9,020 mGy.

Thyroid doses by category of cleanup workers are presented in Table 11. For one study subject who was a staff member of the Kurchatov Institute, thyroid dose was estimated to be 1,010 mGy. The highest exposure categories of cleanup workers included liquidators who worked at the Chernobyl site several times as members of different categories, the mixed category in Table 11 (mean total dose = 471 mGy), staff of construction group AC-605 (206 mGy), and military cleanup workers (138 mGy). Representatives of these three categories (early cleanup workers, military cleanup workers, and mixed) received thyroid doses from inhalation of ^{131}I and short-lived radionuclides as they started the cleanup mission during period between 26 April and 6 May 1986.

Table 12 provides the distribution of thyroid dose due to different exposure pathways for the study subjects. Most

Table 5. Parameters of RADRUE model and their distributions used to calculate individual stochastic thyroid doses due to external irradiation and inhalation of ^{131}I and short-lived radionuclides which were considered to be shared (subject related).

Parameter					
Description	Symbol	Unit	Central value (arithmetic mean [AM])	Distribution	Reference
Duration of performance of cleanup mission task	Δt_j	d	AM and CV[a] from database	U((1 − CV) × AM, (1 + CV) × AM)[b] or U(0.9 × AM, 1.1 × AM)	Kryuchkov et al. 2009
External irradiation					
Exposure rate in air	$P[x(t_j),y(t_j)]$	mGy h^{-1}	AM and GSD from database	TLN(GM[c], GSD, GSD^{-2} × GM, GSD^2 × GM)[d]	Kryuchkov et al. 2009
Conversion coefficient from exposure rate in air to the thyroid dose	C_{th}	mGy h^{-1} per mGy h^{-1}	0.739	TN(AM, 0.1 × AM, AM − 2 × SD, AM + 2 × SD)[e]	Expert judgement
Shielding factor	L_j	Unitless	Table 2 from Kryuchkov et al. 2009	TN(AM, 0.25 × AM, AM − 2 × SD, AM + 2 × SD)	Kryuchkov et al. 2009
Inhalation of ^{131}I and short-lived radionuclides					
^{131}I concentration in air	C_{air}^{I-131}	kBq m^{-3}	AM and GSD from database	TLN(GM[c], GSD, GSD^{-2} × GM, GSD^2 × GM)[d]	Talerko 2005b
Ventilation rate	B_m	m^3 d^{-1}	ICRP 2002	TLN(0.94 × AM, 1.4, 0.5 × GM, 2 × GM)	Goosens et al. 1998
Thyroid mass	m_{th}	g	20	TLN(0.94 × AM, 1.4, 0.5 × GM, 2 × GM)	Likhtarov et al. 2013
Fraction of inhaled iodine transferred to blood	w_{inh}	Unitless	0.66	TR(0.5, 0.66, 0.82)[f]	ICRP 1995
Fraction of iodine uptake by thyroid	w_{th}	Unitless	0.3	TR(0.2, 0.3, 0.4)	ICRP 1993
Biological half-time of iodine removal from the thyroid	T_b	d	89	TR(76, 89, 102)	ICRP 1993

[a]CV: coefficient of variation, CV = AM/SD.

[b]U(min, max): uniform distribution with the following parameters: minimal value (min), maximal value (max).

[c]$GM = AM \times \left[\sqrt{e^{(\ln(GSD))2}}\right]^{-1}$ (derived from Carroll et al. 2006); GM: geometric mean; AM: arithmetic mean; GSD: geometric standard deviation.

[d]TLN(GM, GSD, min, max): truncated lognormal distribution with the following parameters: geometric mean (GM), geometric standard deviation (GSD), minimal value (min), maximal value (max).

[e]TN(AM, SD, min, max): truncated normal distribution with the following parameters: arithmetic mean (AM), standard deviation (SD), minimal value (min), maximal value (max).

[f]TR(min, mode, max): triangular distribution with the following parameters: minimal value (min), mode of distribution (mode), maximal value (max).

Table 6. Selected parameters of dosimetry model to calculate thyroid dose due to ^{131}I intake during residence which were considered to be shared (subject independent).

Parameter			Central value (arithmetic mean [AM])	Distribution	Shared among subjects	Reference
Description	Symbol	Unit				
Daily deposition of ^{131}I	$GD_{I\text{-}131}$	kBq m^{-2}	database	TLN(0.9 × AM, 1.6, 0.4 × GM, 2.6 × GM)[a]	Living in the same settlement	Talerko 2005b
Coefficient of ^{131}I interception by grass	f	Unitless	0.19	TLN(0.94 × AM, 1.4, 0.5 × GM, 2 × GM)	Living in the same settlement	Prister 2008
Removal rate of ^{131}I from grass	λ_{gr}	d^{-1}	0.15	TR(0.13, 0.15, 0.17)[b]	All	Arefieva et al. 1988
Pasture grass yield	Y_{gr}	kg m^{-2}	0.75	TR(0.5, 0.75, 1.0)	All	Likhtarov et al. 2014
Soil per unit of ground	Y_{soil}	kg m^{-2}	1.0	TR(0.3, 1.0, 1.5)	All	Korobova et al. 2010
Consumption of grass by cow	I_{gr}	kg d^{-1}	45	TR(30, 45, 60)	All	Likhtarov et al. 2014
Consumption of soil by cow	I_{soil}	kg d^{-1}	0.55	TR(0.4, 0.55, 0.7)	All	Pröhl et al. 2005
Rate of biological elimination of ^{131}I from cow's milk	λ_b	d^{-1}	1.0	TR(0.5, 1.0, 1.74)	All	Müller and Pröhl 1993
Feed to cow's milk transfer factor for ^{131}I	TF_m	d L^{-1}	0.01	TLN(0.0065, 2.5, 0.001, 0.04)	All	Likhtarov et al. 2014
Raion-specific scaling factor	SF_l	Unitless	Table 3	TLN(GM, GSD, GSD^{-1} × GM, GSD × GM)	Living in the same raion	Likhtarov et al. 2005
Parameters of fitting function (eqn [13]):						
Rural settlement	B	Unitless	0.59 (GM)	TLN(0.59, 1.1, 0.54, 0.65)	Living in the same settlement	Likhtarov et al. 2005
	β	Unitless	0.36	TN(0.36, 0.1, 0.26, 0.46)[c]	Living in the same settlement	Likhtarov et al. 2005
Urban settlement	B	Unitless	0.36 (GM)	TLN(0.36, 1.5, 0.24, 0.54)	Living in the same settlement	Likhtarov et al. 2005
	β	Unitless	0.61	TN(0.61, 0.11, 0.50, 0.72)	Living in the same settlement	Likhtarov et al. 2005

[a]TLN(GM, GSD, min, max): truncated lognormal distribution with the following parameters: geometric mean (GM), geometric standard deviation (GSD), minimal value (min), maximal value (max).

[b]TR(min, mode, max): triangular distribution with the following parameters: minimal value (min), mode of distribution (mode), maximal value (max).

[c]TN(AM, SD, min, max): truncated normal distribution with the following parameters: arithmetic mean (AM), standard deviation (SD), minimal value (min), maximal value (max).

Table 7. Selected parameters of dosimetry model to calculate thyroid dose due to ^{131}I intake during residence which were considered to be unshared (subject related).

Parameter			Central value		
Description	Symbol	Unit	(geometric mean [GM])	Distribution	Reference
Relative time-integrated activity of ^{131}I in the thyroid					
Rural settlement	RA_I	Unitless	1.07	TLN (1.07, 2.1, 0.51, 2.2)[a]	Likhtarov et al. 2005
Urban settlement	RA_I	Unitless	1.1	TLN (1.1, 3.0, 0.37, 3.3)	Likhtarov et al. 2005

[a] TLN(GM, GSD, min, max): truncated lognormal distribution with the following parameters: geometric mean (GM), geometric standard deviation (GSD), minimal value (min), maximal value (max).

subjects (390; 64.3% of the total) received low doses to the thyroid, less than 100 mGy from all exposure pathways combined; the median contribution of internal irradiation to the total thyroid dose in this group was about 60%. In all, 20 study subjects (3.3% of the total) received thyroid doses of 1,000 mGy or higher, mainly due to external irradiation (Fig. 5). For the subject with maximal thyroid dose in the study (9,020 mGy), exposure to ^{131}I was estimated to be 5,110 mGy (57% of the total dose), including 1,680 mGy due to inhalation during the cleanup mission and 3,430 mGy during residence (Fig. 5).

Uncertainties in thyroid doses

Sets of multiple individual stochastic doses were calculated for each study subject: 10,000 doses due to external irradiation, 10,000 doses due to inhalation of ^{131}I, 10,000 doses due to inhalation of short-lived radionuclides, and 1,000 doses due to ^{131}I intake during residence. Fig. 6 shows, for example, a normal probability plot of individual stochastic doses (logarithm of values) due to different exposure pathways calculated for one of the study subjects. Distribution of individual stochastic doses was found to be lognormal and the geometric standard deviation (GSD) characterizes the uncertainty in the doses.

Table 13 shows distributions of the GSDs attached to individual stochastic thyroid doses calculated in this study. The GSDs of individual stochastic doses due to external irradiation varied from 1.2 to 6.9 with a mean equal to 2.0. For almost half of the study subjects, the GSDs of individual stochastic doses due to external irradiation vary between

Table 8. Sources of unshared errors of dosimetry model to calculate thyroid dose due to ^{131}I intake during residence that was associated with information from the personal interview.

Parameter				
Description	Symbol	Unit	Central value	Distribution
Imprecise date of relocation, change of consumption habits, or administration of stable iodine				
Answer: "End of April"	—	—	28 April	DU(27, 28, 29, 30 April)[a]
Answer: "Beginning of May"	—	—	5 May	DU(1, 2, 3, 4, 5, 6, 7, 8, 9, 10 May)
Answer: "Middle of May"	—	—	15 May	DU(11, 12, 13, 14, 15, 16, 17, 18, 19, 20 May)
Answer: "End of May"	—	—	25 May	DU(21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 May)
Answer: "June"	—	—	15 June	DU(1–30 June by 1 d)
Date of stable iodine administration	—	—	Questionnaire	B(0.5)[b]
Consumption rate				
Consumption rate of cow's milk, milk from shop, milk products (milk in soup, sour milk, sour cream, soft cottage cheese, kefir), and leafy vegetables reported during personal interview	$V_{n,k}$	L d^{-1} kg d^{-1}	Questionnaire	TR(0.75 × AM, AM, 1.25 × AM)[c]
Imprecise consumption rate				
Response: "I did consume (*foodstuff*), but I do not remember how much (*foodstuff*) I consumed"	$V_{n,k}$	L d^{-1} kg d^{-1}	Table 9	TLN(GM, GSD, GSD^{-2} × GM, GSD^2 × GM)[d]
Response: "I do not remember if I consumed (*foodstuff*)"	$V_{n,k}$	L d^{-1} kg d^{-1}	P_{cons} × AM (Table 9)	TLN(GM, GSD, GSD^{-2} × GM, GSD^2 × GM) with probability of B(P_{cons})

[a] DU(a_1, a_2, …, a_n): discrete uniform distribution that returns a_1, a_2, …, a_n with equal probability of n^{-1}.

[b] B(p): Bernoulli distribution that returns "1" with probability (P_{cons}) and returns "0" with probability ($1 - P_{cons}$).

[c] TR(min, mode, max): triangular distribution with the following parameters: minimal value (min), mode of distribution (mode), maximal value (max).

[d] TLN(GM, GSD, min, max): truncated lognormal distribution with the following parameters: geometric mean (GM), geometric standard deviation (GSD), minimal value (min), maximal value (max).

Table 9. Fraction of consumers (P_{cons}), arithmetic mean (AM), geometric mean (GM), and geometric standard deviation (GSD) of consumption rates of foodstuff used for imputation of imprecise responses provided during the personal interviews.

		Consumption rate, L d^{-1} (kg d^{-1})		
Food	P_{cons}	AM	GM	GSD
Rural settlements				
Private cow's milk	0.629	0.56	0.40	2.4
Shop milk	—	—	—	—
Sour milk, kefir	0.443	0.19	0.13	2.5
Sour cream, soft cheese	0.676	0.075	0.065	2.1
Leafy vegetables	0.792	0.045	0.030	2.4
Mixed rural-urban type of settlements				
Private cow's milk	0.439	0.38	0.20	3.2
Shop milk	0.298	0.16	0.11	2.3
Sour milk, kefir	0.407	0.18	0.085	3.8
Sour cream, soft cheese	0.721	0.065	0.060	2.1
Leafy vegetables	0.866	0.050	0.025	2.4
Urban settlements				
Private cow's milk	—	—	—	—
Shop milk	0.468	0.22	0.20	2.0
Sour milk, kefir	0.476	0.13	0.090	1.9
Sour cream, soft cheese	0.668	0.070	0.065	1.8
Leafy vegetables	0.777	0.030	0.020	2.5

1.5 and 2.0. The largest GSDs (>3.0) were associated with the highest doses and were due to uncertainties in exposure rate grids in highly contaminated locations at the Chernobyl site and in exact duration and location of performance of cleanup mission tasks as reported by the study subject. The GSDs of individual stochastic doses due to ^{131}I inhalation varied from 1.3 to 5.4 with a mean equal to 1.8. For the majority of the study subjects (80%), the GSDs varied between 1.5 and 2.0. The GSDs of individual stochastic doses due to inhalation of short-lived radioiodines and radiotelluriums varied from 1.4 to 14.7 with a mean equal to 2.0. The GSDs of individual stochastic doses due to ^{131}I intake during residence varied from 1.8 to 4.8 with a mean of 2.6.

DISCUSSION

Individual thyroid doses from different exposure pathways were estimated in this study for 607 subjects of a case-control study of thyroid cancer among Chernobyl cleanup workers. Internal exposure of the thyroid from ^{131}I, both during the cleanup mission and during residence, was found to be an important exposure pathway for the Ukrainian cleanup workers, as it contributed more than 50% to the total thyroid dose to 265 out of 592 study subjects (15 out of 607 study subjects were not exposed to either ^{131}I or short-lived radionuclides). Kesminiene et al. (2012) found that ^{131}I intake was the major contributor to the thyroid dose to Belarusian liquidators because they were residents of contaminated settlements and were returning home every evening or after weekly shift work.

Thyroid doses from external and internal (inhalation of ^{131}I and short-lived radionuclides during the cleanup mission and intake of ^{131}I during residence) irradiation are not correlated with each other (r = 0.13). Fig. 7 compares thyroid doses due to internal irradiation with doses due to external irradiation during the cleanup mission for 592 study subjects who were exposed to both pathways.

Uncertainties in thyroid doses

A similar pattern of uncertainties for doses due to external irradiation was found in other case-control studies among Chernobyl cleanup workers that used the RADRUE method for dose calculations: in the Ukrainian-American study of leukemia and related disorders, the mean GSD among 1,000 subjects was found to be 2.0 (Chumak et al. 2015), and the mean GSD was found to be 1.9 among 357 and 530 subjects of the International Agency for Research on Cancer (IARC)-coordinated studies of hematological malignancies (Kesminiene et al. 2008) and of thyroid cancer (Kesminiene et al. 2012), respectively.

It should be noted that the RADRUE methodology takes into account only the so-called intrinsic uncertainty; e.g., uncertainty in the dose rate data due to interpolation and extrapolation and uncertainty in the expert dosimetrist's decisions while converting the questionnaire data into personal histories with RADRUE data format. So-called questionnaire-based or human factors uncertainty that is associated with uncertainty in recollection and reporting of the events related to the cleanup activities of the study subject by himself or by proxies is not quantified by RADRUE methodology (Kryuchkov et al. 2009).

Table 10. Thyroid doses from different exposure pathways reconstructed for study subjects of case-control study.

	Thyroid dose[a] (mGy) due to				
Parameter	External irradiation	Inhalation of ^{131}I during the mission	Inhalation of short-lived radionuclides during the mission	Intake of ^{131}I during residence	Total
N	607	200	198	587	607
Arithmetic mean	140	44	11	42	199
Median	20	12	1.6	7.3	47
Range	0.015–3,630	~0–1,680	~0–377	0.001–3,430	0.15–9,020

[a]Arithmetic mean, median, and range of thyroid doses are given for *N* study subjects who were exposed to the given exposure pathway. Therefore, arithmetic mean of total dose does not equal the sum of arithmetic means of components of the dose.

Table 11. Thyroid doses due to all exposure pathways by category of cleanup workers included in the case-control study.

		Thyroid dose (mGy) due to									
		External irradiation		Inhalation of ^{131}I during the mission		Inhalation of short-lived radionuclides during the mission		Intake of ^{131}I during residence		Total	
Category of cleanup workers	Number of subjects	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Early cleanup workers	64	68	0.24–867	20	~0–194	5.0	~0–59	17	0.22–109	100	~0–891
Chernobyl NPP personnel	1	68	—	—	—	—	—	5.9	—	74	—
Sent to assist the Chernobyl NPP staff	4	108	0.32–375	—	—	—	—	12	5.1–29	120	20–385
Staff of AC-605	6	200	3.9–788	—	—	—	—	6.7	1.7–24	206	6.7–790
Staff of Kurchatov Institute	1	1,010	—	—	—	—	—	3.0	—	1,010	—
Military	236	121	0.14–1,670	32	~0–277	6.5	~0–78	8.5	0.04–102	138	0.53–1,670
Sent on mission	137	24	0.01–755	2.3[a]	—	0.21	—	24	0.24–808	47	0.7–820
Staff of "Combinat"	6	36	0.15–187	—	—	—	—	40	8.9–122	70	0.15–196
Mixed[b]	152	299	0.28–3,630	57	~0–1,680	15	~0–377	122	0.001–3,430	471	1.5–9,020
Entire study	607	140	0.015–3,630	44	~0–1,680	11	~0–377	42	0.001–3,430	199	0.15–9,020

[a]One study subject was exposed to inhalation of ^{131}I and short-lived radionuclides.

[b]Mixed refers to a set of liquidators who worked at the Chernobyl site several times as members of different categories.

Table 12. Distribution of thyroid dose due to different exposure pathways for the study subjects.

Interval of thyroid dose (mGy)	External irradiation		Inhalation of ^{131}I during the mission		Inhalation of short-lived radionuclides during the mission		Intake of ^{131}I during residence		Total	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
<0.1	10	1.6	13	6.5	45	22.7	6	1.0	—	—
0.1–0.99	92	15.2	30	15.0	46	23.2	33	5.6	6	1.0
1.0–9.99	156	25.7	55	27.5	52	26.3	322	54.9	105	17.3
10–99.99	179	29.5	82	41.0	54	27.3	195	33.2	279	46.0
100–999.99	156	25.7	19	9.5	1	0.5	28	4.8	197	32.4
≥1,000	14	2.3	1	0.5	—	—	3	0.5	20	3.3
Entire study	607	100.0	200	100.0	198	100.0	587	100.0	607	100.0

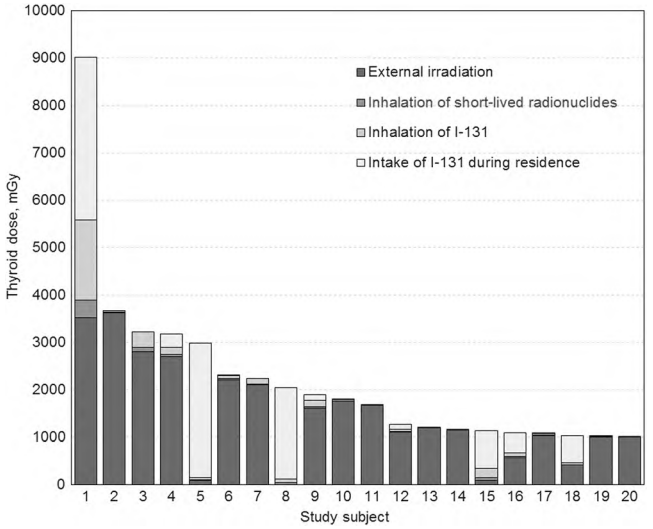

Fig. 5. Contribution of different exposure pathways to thyroid dose of 20 study subjects who received doses of 1,000 mGy or higher.

Estimation of the human factor uncertainty is the subject of a separate study.

In addition, all parameters of dosimetry models in the RADRUE methodology were considered to be sources of unshared errors. Although, as was mentioned above, a fraction of shared dose caused by the situation when the study subjects shared the same location at the same time was estimated to be small (<1%), there are other possible sources of shared errors that were not considered; for example, errors associated with extrapolation in time and space of exposure rate measurements to create grids of ambient exposure rate in computer code Rockville. The same comment applies to ^{131}I concentration in air.

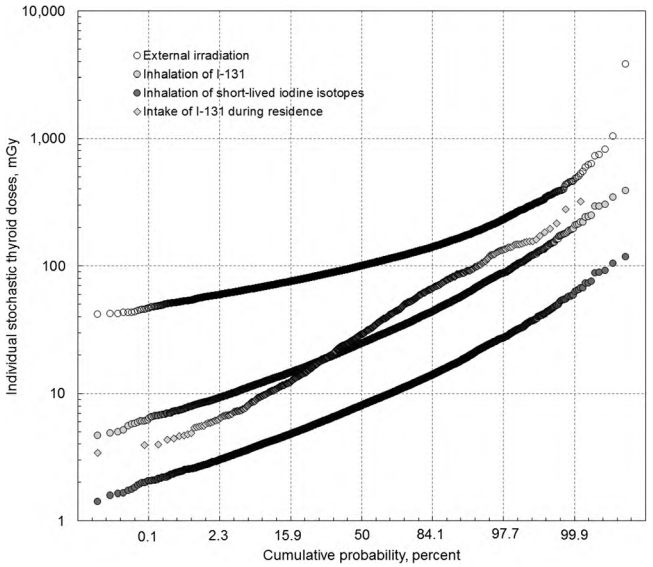

Fig. 6. Normal probability plot of individual stochastic doses (logarithms) due to different exposure pathways calculated for the study subject.

Table 13. Distributions of the geometric standard deviations (GSDs) attached to individual stochastic thyroid doses.

GSD interval	External irradiation during the mission			Inhalation of ^{131}I during the mission			Inhalation of short-lived radionuclides during the mission			Intake of ^{131}I during residence		
	N	%	Mean dose (mGy)	*N*	%	Mean dose (mGy)	*N*	%	Mean dose (mGy)	*N*	%	Mean dose (mGy)
<1.5	96	15.8	183	12	6.0	47	7	3.5	7.2	—	—	—
1.5–1.99	291	47.9	105	160	80.0	38	156	78.9	11	8	1.4	5.3
2–2.49	125	20.6	129	22	11.0	91	24	12.1	20	290	49.4	33
2.5–2.99	49	8.1	158	4	2.0	10	4	2.0	0.2	231	39.4	42
3–3.49	18	3.0	361	1	0.5	1.2	1	0.5	14	55	9.4	92
≥3.5	28	4.6	244	1	0.5	0.01	6	3.0	1.2×10^{-4}	3	0.5	4.2
Entire study	607	100.0	140	200	100.0	44	198	100.0	11	587	100.0	42

Larger uncertainty in doses due to ^{131}I intake during residence was observed in our study in comparison with the IARC-coordinated study of thyroid cancer in Chernobyl cleanup workers. In the IARC study, GSDs of residential doses due to ^{131}I intake varied from 1.9 to 2.5 with a mean of 2.2 (Kesminiene et al. 2012). This can be expected as individual doses were estimated in this study based on personal interview data on consumption of milk, milk products, and leafy vegetables. In the study of Kesminiene et al. (2012), individual thyroid doses represented settlement-average doses at the subject's residence, as no information was collected for the study subjects on individual consumption around the time of the accident.

Validation of thyroid doses due to ^{131}I intake during residence

There are no subjects with direct thyroid measurements in this study. However, 70 study subjects resided during 26 April–30 June 1986 in 33 Ukrainian settlements and 1 Belarusian settlement where direct thyroid measurements were performed on other individuals. Estimated in this study, individual residential thyroid doses due to ^{131}I intake for 70 subjects were compared with mean thyroid doses in settlements of residence derived from direct thyroid measurements conducted among adults and young adolescents (Fig. 8). As can be seen from the figure, the two sets of doses agree for 94.3% individuals within a factor of 3 (shown by broken lines); the coefficient of correlation is $r = 0.87$. The mean of the ratios of thyroid doses estimated using the model to the settlement-average thyroid doses derived from direct thyroid measurements was 1.1 ± 0.8, and the median of ratios was 0.9. It should be noted that the study subjects who reported they did not consume any locally produced food were excluded from the validation exercise, as settlement-average thyroid doses derived from direct thyroid measurements reflect typical behavior of the measured population (including consumption of local cow's milk, milk products, and/or leafy vegetables), not only inhalation intake of ^{131}I.

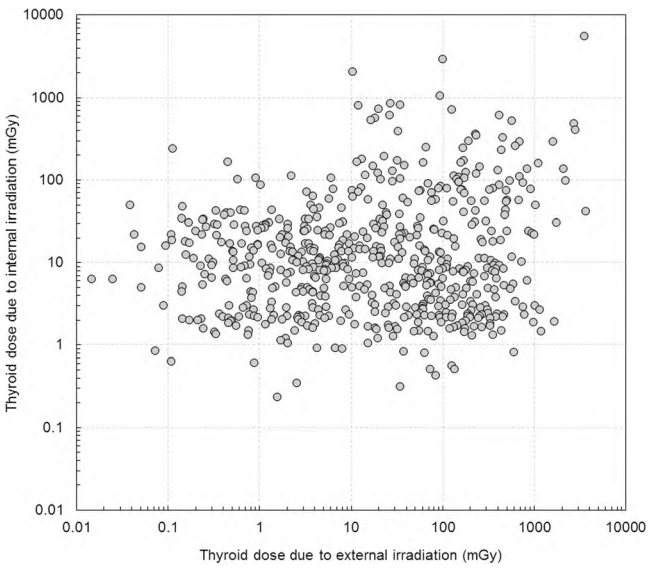

Fig. 7. Comparison of thyroid doses to 592 study subjects: internal irradiation vs. external irradiation.

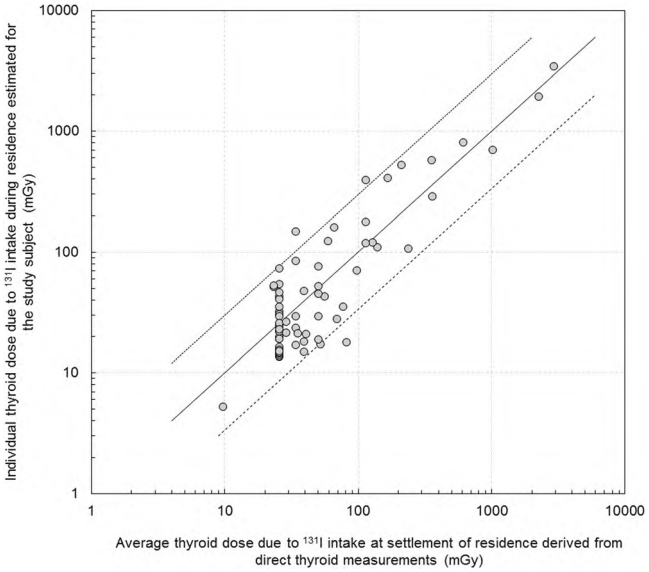

Fig. 8. Comparison of residential thyroid dose from ^{131}I intake: calculated in this study for 70 study subjects and mean thyroid doses in settlements of residence derived from direct thyroid measurements. Broken lines show factor of 3 difference between two sets of doses.

CONCLUSION

Individual thyroid doses were estimated for 607 subjects in a case-control study of thyroid cancer among Ukrainian cleanup workers of the Chernobyl accident. Thyroid doses were calculated for different exposure pathways, including external irradiation and inhalation of ^{131}I and short-lived ^{132}I, ^{133}I, ^{135}I, ^{131m}Te, and ^{132}Te during the cleanup mission at the Chernobyl site as well as intake of ^{131}I during residence in contaminated settlements. It should be noted that internal exposure of the thyroid from ^{131}I was found to be an important exposure pathway for the Ukrainian Chernobyl cleanup workers, as it contributed more than half to the total thyroid dose in 45% of the study subjects. Also, it was found there is no correlation between thyroid dose due to inhalation and due to external irradiation, which dictates the need for separate estimation of those components of thyroid dose. The models used in this study to calculate doses were validated against instrument measurements done after the accident. Implementation of dose calculations was based on detailed data on location and timing of different activities during cleanup worker mission as well as information on residential history and consumption of locally produced food during residence, all of which

was collected by personal interviews. Results of the models' development and validation led us to conclude that thyroid doses could be estimated with a reasonable degree of reliability some 30 y after the accident for use in an epidemiological study of thyroid cancer among Chernobyl cleanup workers.

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■■

5. ЕПІДЕМІОЛОГІЧНИЙ АНАЛІЗ ДАНИХ ТА ВИЗНАЧЕННЯ ДОЗО ЗАЛЕЖНИХ РИЗИКІВ

5-й розділ присвячено результатам статистичного аналізу дозо залежних ризиків лейкемії за періоди 1986–2000 та 1986–2006 та РЩЗ за період 1986-2012. Окремо аналізувався вплив можливих модифікуючих факторів на ризик виникнення лейкемії.

Статистичний аналіз ризиків лейкемії **(підрозділ 5.1)** було проведено застосовуючи модель умовної логістичної регресії (conditional regression model), передбачаючи лінійну залежність доза-ефект шляхом максимальної правдоподібності (maximum likelihood), використовуючи PECAN модуль статистичного пакету EPICURE.

Використовувалась модель надлишку відносного ризику.

Risk = background risk x (1.0 + β dose exp [Σi γi Zi]), (1),

В якій β – ERR на Гр опромінення (ERR / Gy), Zi являє собою потенційні модифікуючі фактори, а γi - їх відповідні параметри.

Розрахований (ERR/Gy) для лейкемії в цілому в 1986–2000 рр склав 3.44; 95% CI: 0.47 – 9.78, p<0.01, в тому числі для ХЛЛ (ERR/Gy = 4.09; 95% CI: не визн.–14.41) і для не-ХЛЛ групи лейкемій (ERR/Gy = 2.73; 95% CI: не визн.–13.50)

Було визначено лінійну достовірну позитивну асоціацію між кумулятивною дозою опромінення на червоний кістковий мозок з урахуванням 2-хрічного лаг-періоду з надлишком відносного ризику виникнення лейкемії впродовж 1986–2006 рр. на 1 Грей опромінення (ERR/Gy) на рівні 1.26 (95 % ДІ: 0.03–3.58, p = 0,04)

З подальшого аналізу було виключено 20 випадків з атиповим індивідуальним ризиком. Доза-відповідь ефект для решти 117 випадків був

подібним, склав 2,38 з 95 % ДІ від 0,49 до 5,87 та p=0,004, і мав позитивні значення як для ХЛЛ (ERR/Gy=2.58, 95% ДІ 0.02–8.43 і p=0.047), так і для не–ХЛЛ групи лейкемій (ERR/Gy=2.21, 95% ДІ 0.05–7.61 і p=0.039 **(підрозділ 5.2).**

Популяційний атрибутивний ризик виникнення лейкемії (PAR) склав 16,4 % (95 % ДІ: 3.9–32.6)

Окрему увагу (**підрозділ 5.3**) було приділено врахуванню впливу потенційних модифікуючих ризик факторів нерадіаційної природи. Було досліджено ефекти впливу професійної експозиції до пестицидів, органічних розчинників, інших потенційно небезпечних хімічних речовин, роботи на небезпечних виробництвах в цілому. Не було встановлено суттєвого впливу експозиції до названих факторів на ризик виникнення лейкемії. Єдиним фактором, вплив якого потенційно можна оцінити як досить суттєвий для виникнення лейкемії, було визначено професійний контакт із бензином. При цьому встановлено, що надлишок ризику спостерігається за рахунок хронічних мієлоїдних форм лейкемії.

Перші результати аналізу ризиків РЩЗ **(підрозділ 5.4)** констатують, що у когорті учасників ЛНА (150 813) визначено надлишок відносного ризику виникнення рака щитоподібної залози впродовж 1986-2012 рр. (ERR/Gy=0.40; 95% ДІ: -0.05, 1.48; p=0.12). Інформаційнипй масив для остаточного розрахунку ризиків раку щитоподібної залози підготовлений, розрахунки виконані і внесені в рукопис манускрипту, який прийнято до друку в European Journal of Epidemiology і буде опубліковано найближчим часом.

5.1 Українсько-американське дослідження лейкемії та споріднених захворювань серед учасників ліквідації наслідків аварії на ЧАЕС з України: III. Радіаційні ризики (1986-2000 рр.)

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The Ukrainian-American Study of Leukemia and Related Disorders among Chornobyl Cleanup Workers from Ukraine: III. Radiation Risks

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Leukemia is one of the cancers most susceptible to induction by ionizing radiation, but the effects of lower doses delivered over time have not been quantified adequately. After the Chornobyl (Chernobyl) accident in Ukraine in April 1986, several hundred thousand workers who were involved in cleaning up the site and its surroundings received fractionated exposure, primarily from external γ radiation. To increase our understanding of the role of protracted low-dose radiation exposure in the etiology of leukemia, we conducted a nested case-control study of leukemia in a cohort of cleanup workers identified from the Chornobyl State Registry of Ukraine. The analysis is based on 71 cases of histologically confirmed leukemia diagnosed in 1986–2000 and 501 age- and residence-matched controls selected from the same cohort. Study subjects or their proxies were interviewed about their cleanup activities and other relevant factors. Individual bone marrow radiation doses were estimated by the RADRUE dose reconstruction method (mean dose = 76.4 mGy, SD = 213.4). We used conditional logistic regression to estimate leukemia risks. The excess relative risk (ERR) of total leukemia was 3.44 per Gy [95% confidence interval (CI) 0.47–9.78, $P < 0.01$]. The dose response was linear and did not differ significantly by calendar period of first work in the 30-km Chornobyl zone, duration or type of work. We found a similar dose–response relationship for chronic and non-chronic lymphocytic leukemia [ERR = 4.09 per Gy (95% CI < 0–14.41) and 2.73 per Gy (95% CI < 0–13.50), respectively]. To further clarify these issues, we are extending the case-control study to ascertain cases for another 6 years (2001–2006).

INTRODUCTION

Studies of individuals exposed to moderate doses of radiation, generally at high dose rates, such as survivors of the atomic bombings in Japan have demonstrated that leukemia is one of the cancers most susceptible to induction by ionizing radiation and that it can occur very soon after radiation exposure (*1–3*). However, there remains considerable interest in the relationship between protracted exposure to low doses of radiation and leukemia, because these types of exposure are most likely to be encountered by the general public and radiation workers (*1*).

The accident at the Chornobyl (Chernobyl) nuclear power plant in northern Ukraine in April 1986, as well as being a public health, social and economic disaster for the countries most affected, also provided an opportunity to evaluate the relationship between leukemia and low-dose and low-dose-rate radiation (*4*). After the accident, several hundred thousand workers who were involved in cleaning up the site and its surroundings received fractionated whole-body doses, primarily from external radiation (*1*). To date, only studies of workers from the Russian Federation have attempted to quantify the risk of leukemia among Chornobyl cleanup workers (*5–8*). Data from these studies suggest an association between leukemia and radiation exposure, but the magnitude of the radiation effect is unclear due to substantial uncertainty in dose estimates (*1*). Buzunov *et al.* reported an increased risk of leukemia among Ukrainian cleanup workers, but dose estimates were not available and evaluation was based only on the year first worked at the accident site (*9*).

To increase our understanding of the role of protracted

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TABLE 1
Distribution of Cases of Leukemia among Ukrainian Chornobyl Cleanup Workers by Cell Type, 1986–2000

Cell type	Cases confirmed by the International Hematology Panel	Cases with estimated doses (percentage confirmed cases)
Acute lymphocytic leukemia	4	3 (75.0)
Acute myeloid leukemia	6	5 (83.3)
Acute leukemia otherwise not specified	9	6 (66.7)
Chronic myeloid leukemia	15	14 (93.3)
Other chronic leukemia[a]	4	4 (100)
Subtotal non-CLL[b]	38	32 (84.2)
CLL	49	39 (79.6)
Total	87	71 (81.6)

[a] These cases were identified as large granular lymphocytic leukemia and were verified by immunophenotypic surface markers as two cases of the T-cell type and two cases of the NK-cell type.

[b] Chronic lymphocytic leukemia.

low-dose radiation exposure in the etiology of leukemia, we conducted a nested case-control study of leukemia in Ukrainian cleanup workers.

MATERIALS AND METHODS

We provided a full description of the study in the first paper in this series (*10*) that we briefly summarize below.

Cases

We identified a cohort of 110,645 workers from the Chornobyl State Registry of Ukraine (SRU) who participated in Chornobyl cleanup activities before 1991 and who were initially registered in one of five oblasts[3] (Chernihiv, Cherkasy, Kharkiv, Kyiv and Dnipropetrovsk) or Kyiv City. The selected geographical area allowed for easy access by study investigators and included a large number of cleanup workers. The cohort represents 46% of all cleanup workers included in the SRU.

We ascertained potential cases of leukemia occurring within the cohort between 1986 and 2000 through computerized linkage (*11*) of cohort records and a Provisional Leukemia Registry (*10*). We established an expert international panel of five hematologists and hematopathologists to review all diagnoses (*12*). The Panel was given 128 potential leukemia cases to review [111 with a preliminary diagnosis of leukemia and 17 with a preliminary diagnosis of myelodysplastic syndrome (MDS)], and they confirmed 87 cases of leukemia (Table 1) and six cases of MDS. The Panel initially classified the leukemia cases using the French-American-British (FAB) system but changed to the WHO system of classification in 2007 (*13*). Complete medical records, including a description of the histological confirmation of the diagnosis, were available for all cases. In 56 (64.4%) of 87 confirmed cases, diagnosis was supported by biological material. Sixteen cases were excluded from risk analysis because their doses could not be calculated reliably (two proved to be ineligible, seven could not be traced, four refused to complete the dosimetry questionnaire, and for three the quality of interview was inadequate). Thus our analysis included 71 cases of the 87 (81.6%) confirmed cases of leukemia, and, as shown in Table 1, this participation rate was similar for all leukemia cases excluding chronic lymphocytic leukemia (CLL) and CLL cases separately ($P = 0.58$). Participating cases ranged in age at diagnosis from 25 to 69 years (median = 49). Separate analyses of the MDS dose response could not be performed due to the small number of cases.

Due to the high mortality rate of leukemia patients and since we conducted interviews between 2002 and 2004 for cases diagnosed in 1986–2000, we had to interview proxy respondents for 60% of case subjects, mainly next-of-kin for personal, residential and medical history and coworkers for Chornobyl work history. In contrast, since most control subjects were alive, we relied on proxy interviews for only 7.2%.

Controls

For each potential leukemia case, to achieve a 5:1 matching ratio, we randomly selected five to nine control subjects from members of the cohort who were alive and at risk at the time of the case's diagnosis (incidence density sampling) and matched on oblast or Kyiv City and year of birth. Of the selected 792 controls, 536 were interviewed, 101 refused to participate, 133 could not be traced, and 22 moved out of the study regions (response rate of 71.6% for alive controls, 60.2% for next-of-kin, and 66.1% for colleagues responding for deceased controls). Of the interviewed controls, 348 were originally selected for 71 confirmed leukemia cases and the remaining 188 controls had been selected and interviewed for cases that were not included in the study because their initial diagnosis was not confirmed by the study hematologist, their final diagnosis was not confirmed by the international panel, or they did not participate in this study. We attempted to match the latter group of controls to the 71 confirmed cases, but only 153 (81.3%) could be matched; thus the total number of controls used in this analysis is 501. Analyses with and without these additional 153 controls showed essentially similar results, but the additional controls improved the precision of analyses. Match on year of birth was achieved for 442 controls (88.2%). The remaining controls were matched within 2 years of birth ($n = 35$ or 7.0%) or within 5 years of birth ($n = 24$ or 4.8%).

Dosimetry

The RADRUE dosimetry method was used to estimate individual Chornobyl-related bone marrow doses for all cases and controls (*14*). The method uses detailed interviews with study subjects or, if they were deceased, with their next-of-kin for demographic and medical data and coworker proxies for the details of cleanup activities, carried out by trained interviewers to ascertain Chornobyl work and residential history. The interview included questions on workers' activities during cleanup, location of places of work and residence, types of work, transportation routes to and from work, and corresponding dates. An expert dosimetrist used the questionnaire data in combination with a database of field exposure measurements to estimate the total Chornobyl-related dose for each subject (including both cleanup activities and residence in the highly contaminated areas). Investigators have tested and validated the RADRUE dose estimation methodology (*14*).

The RADRUE method was used to calculate 10,000 annual bone marrow dose estimates for 1986–1990 (all cleanup work ceased in 1990) for each study subject by generating 10,000 realizations of a dose prediction equation by random sampling from assumed distributions of model parameters.

Statistical Analysis

We used standard conditional logistic regression for matched sets for all analyses. We computed odds ratios (OR) to estimate relative risks (RR) in four dose categories (0–1.9, 2.0–19.9, 20.0–149.9, 150.0–3220 mGy) based on the categorization of the case dose distribution approximately into quarters. We fit an excess relative risk (ERR) model for continuous doses,

$$\text{Risk} = \text{background risk} \times \left(1.0 + \beta\ \text{dose} \exp\left[\sum_i \gamma_i Z_i\right]\right), \quad (1)$$

[3] Oblast is an administrative unit similar in size to a state or province.

TABLE 2
Descriptive Characteristics of Cases and Controls Identified from the Cohort of Ukrainian Chornobyl Cleanup Workers during Follow-up (1986–2000)

	Cases	%	Controls	%	*df*[a]	*P* value[b]
Total	71	100.0	501	100.0		
Year of birth					4	0.89
1923–1929	4	5.6	35	7.0		
1930–1939	24	33.8	144	28.7		
1940–1949	18	25.4	149	29.7		
1950–1959	21	29.6	146	29.1		
1960–1965	4	5.6	27	5.4		
Areas of study					5	0.89
Cherkasy oblast	3	4.2	40	8.0		
Chernihiv oblast	6	8.5	44	8.8		
Dnipropetrovsk oblast	16	22.5	96	19.2		
Kharkiv oblast	8	11.3	67	13.4		
Kyiv oblast	14	19.7	102	20.4		
Kyiv City	24	33.8	152	30.3		
Type of residence					1	0.69
Urban	52	73.2	405	80.8		
Rural	14	19.7	96	19.2		
Unknown	5	7.0	0	0		
Education					3	0.33
8 years or less	9	12.7	74	14.8		
High school	21	29.6	210	41.9		
Trade school	18	25.4	112	22.4		
College	18	25.4	102	20.4		
Unknown	5	7.0	3	0.6		
Proxy interviews					1	<0.01
No	29	40.8	465	92.8		
Yes	42	59.2	36	7.2		

[a] *df*, degrees of freedom from the χ^2 test.
[b] *P* value of the χ^2 test.

where β is the ERR per Gy, Z_i represents potential modifying factors, and γ_i represents their corresponding parameters. In this equation, the effect of dose multiplies the background risk, and by adding 1.0 to the ERR, one obtains the relative risk at 1 Gy. Model 1 is a linear model in dose, although we evaluated several alternative forms, including linear-quadratic, power and exponential models. For these analyses, we used the PECAN module from the EPICURE suite of programs (*15*) to derive point and confidence interval (CI) estimates for all parameters based on maximum likelihood estimation procedures and used likelihood ratio tests for tests of hypotheses. All *P* values are two-sided. We conducted analyses for all leukemias and separately for CLL and non-CLL.

We investigated calendar period first worked in the 30-km Chornobyl zone (categorized into April–May 1986, June–December 1986, 1987 and 1988–1990), duration of mission, i.e., total time worked within the zone (up to 1, 2–3, 4–5 and 6+ months), number of missions (1, 2, 3 and 4+), type of work performed in the zone during the first mission (grouped into early responders, military personnel, professional nuclear power workers and other), as well as smoking (never-, ex- and current smokers of 1–9, 10–19, and ≥20 cigarettes/day), alcohol consumption (never, once a month or less, two or three times a month, once a week, several times a week, every day), education (8 years or less, high school, trade school, higher education), attained age, and urban/rural residence as potential independent risk factors of leukemia after adjustment for radiation exposure. We also investigated possible effects of occupational exposures to chemicals and radiation due to employment in hazardous industries before or after the cleanup work at Chornobyl (yes, no). We retained adjustment variables in the model if they significantly improved the model fit or changed the risk estimate by more than 10%. The percentage of missing information for these variables was very low and did not exceed 4%.

We also evaluated age at first exposure, number of missions within the Chornobyl zone, year of first mission, type of work performed, total duration in the zone, and source of information (subject or proxy respondent) as possible effect modifiers of the dose effect.

The analyses in this report were based on the cumulative doses derived as the sums of the arithmetic means of the annual dose estimates. We assessed lag interval, a period of recent exposure assumed unrelated to disease, for the calculation of cumulative dose from 1986 to 1990 in 1-year increments between 0 and 10 years. The deviance, a measure of model fit, was minimized for both CLL and non-CLL analyses when we set the lag interval to 2 years. We therefore used a lag of 2 years for the calculation of cumulative dose in all analyses. Cumulative doses ranged from 0 to 3220 mGy for cases and from 0 to 2600 mGy for controls (mean = 76.4, SD = 213.4 mGy, 2-year lag). We also conducted several additional exploratory analyses using unlagged annual doses.

RESULTS

Table 2 shows selected descriptive characteristics of study subjects. Case and control subjects did not differ by year of birth, geographic area, type (urban/rural) of residence, or educational level. Among the 71 cases used in the analysis, the International Hematology Panel classified 39 cases as CLL (55%) and 32 as non-CLL (45%).

After adjustment for dose, the odds ratio (OR) by calendar period first worked April/May 1986 was 1.64 relative to first worked between 1988 and 1990, but this difference

TABLE 3
Odds Ratios and 95% Confidence Intervals for all Leukemia by Chornobyl Cleanup Work in the 30-km Zone

	Cases	%	Controls	%	OR[a,b]	95% CI[c]	*df*[d]	*P* value[e]
Calendar period first worked in the 30-km Chornobyl zone							3	0.56
April/May 1986	37	52.1	200	39.9	1.64	0.60–4.45		
June/December 1986	17	23.9	154	30.7	1.06	0.39–2.90		
1987	10	14.1	78	15.6	1.12	0.39–3.18		
1988–1990	7	9.9	69	13.8	1			
Type of work performed in the Chornobyl 30-km zone during the first mission							3	0.93
Early responders	14	19.7	92	18.4	1			
Military personnel	25	35.2	198	39.5	0.88	0.36–2.11		
Professional nuclear power workers	5	7.0	21	4.2	1.15	0.37–3.63		
Other	27	38.0	190	37.9	1.11	0.54–2.31		
Duration of mission, months							3	0.75
≤1	42	59.2	296	59.1	1			
2–3	17	23.9	135	26.9	1.02	0.52–1.98		
4–5	6	8.5	28	5.6	1.70	0.63–4.57		
6+	6	8.5	42	8.4	0.80	0.33–2.23		
Number of missions							3	0.78
1	55	77.5	384	76.6	1			
2	13	18.3	83	16.6	1.08	0.54–2.17		
3	2	2.8	18	3.6	0.64	0.14–2.95		
4+	1	1.4	16	3.2	0.47	0.06–3.66		

[a] Odds ratios for background variables from conditional logistic regression model adjusted for cumulative doses lagged by 2 years.
[b] Cases and controls matched on year of birth and oblast.
[c] Confidence interval.
[d] Degrees of freedom from the likelihood ratio test.
[e] *P* values for test of homogeneity of odds ratios.

was not statistically significant (Table 3). ORs for duration of cleanup work at Chornobyl were close to unity, and there was no clear trend. Similarly, number of missions and type of work performed in the 30-km zone showed no variation in risk after adjustment for dose.

As shown in Table 4, the OR for total leukemia increased with dose categories ($P = 0.03$ for test of linear trend). Although based on few cases, we further divided the highest dose category (Fig. 1) (150.0–3220.0 mGy) into two and found a somewhat higher risk in the upper dose category (OR = 2.21; 95% CI: 0.87–5.57 and OR = 2.89; 95% CI: 1.12–7.46 for categories of 150.0–274.9 and 275.0–3220.0 mGy, respectively). Analyses were also done separately for CLL and non-CLL. Despite the small number of cases, we observed consistent trends for the two subtypes ($P = 0.04$ and 0.25 for test of linear trend, respectively), although the *P* value for the non-CLL cases did not reach statistical significance.

With continuous dose, we estimated an ERR of 3.44 per Gy for all leukemias combined (95% CI: 0.47–9.78, $P < 0.01$) (Table 5). The dose–response parameters for CLL (ERR = 4.09 per Gy; 95% CI: < 0–14.41, $P = 0.079$) and non-CLL (ERR = 2.73 per Gy; 95% CI: < 0–13.50, $P = 0.052$) were consistent. A formal test of homogeneity between the two slopes yielded a *P* value of 0.75, indicating no significant difference in the effects for non-CLL and CLL cases.

We found no evidence that the dose–response estimates for total leukemia or leukemia subtypes were confounded by smoking, alcohol, education, attained age, urban/rural residence, occupation or exposure to chemicals (results not shown). Relatively few subjects worked in hazardous industries, and there was no evidence of a measurable association with employment in such industries and risk of leukemia.

When we excluded subjects with doses above 500 mGy to assess the influence of subjects with extremely high doses, we found a comparable estimate of effect (no. of cases = 67, ERR = 3.54 per Gy, 95% CI: < 0–11.1, $P = 0.08$). The inclusion of quadratic, exponential or power terms in dose did not improve model fit (*P* values of 0.77, 0.73, and 0.33, respectively), indicating no evidence of curvilinearity in the dose response.

To assess the validity of a 2-year lag period, we analyzed the 52 cases diagnosed since 1993 separately (2 years after all cleanup work ceased in 1990). The results were very similar to those for all study subjects, i.e., a statistically significant ERR of more than three per Gy ($P = 0.02$). Comparative analyses of annual doses and cumulative doses lagged by 2 years provided evidence that risk arose primarily from doses received in 1986 (not shown).

Table 5 shows the risk estimates for directly interviewed cases and for deceased cases for whom proxy interviews were necessary. Since there were very few proxy-inter-

TABLE 4
Odds Ratios and 95% Confidence Intervals by Categories of Cumulative Dose and Type of Leukemia

Dose range, mGy[a]	Mean dose, mGy	Cases	%	Controls	%	OR[b,c]	95% CI[d]	*P* value[e]
All cases								
0–1.9	0.6	17	23.9	157	31.3	1		0.03
2.0–19.9	8.8	17	23.9	143	28.5	1.28	0.59–2.75	
20.0–149.9	62.2	20	28.2	131	26.1	1.71	0.80–3.64	
150.0–3220.0	377.4	17	23.9	70	14.0	2.50	1.17–5.33	
Total	76.4	71	100	501	100			
Non-CLL cases								
0–1.9	0.5	8	25.0	76	32.6	1		0.25
2.0–19.9	9.4	8	25.0	65	27.9	1.61	0.49–5.25	
20.0–149.9	66.3	9	28.1	59	25.3	1.95	0.61–6.19	
150.0–3220.0	409.9	7	21.9	33	14.2	2.40	0.72–7.99	
Total	81.6	32	100	233	100			
CLL cases								
0–1.9	0.6	9	23.1	81	32.5	1		0.04
2.0–19.9	8.3	9	33.3	78	29.9	1.07	0.39–2.93	
20.0–149.9	58.7	11	30.8	72	30.2	1.55	0.57–4.21	
150.0–2600.0	349.7	10	12.8	37	7.5	2.60	0.98–6.87	
Total	72.0	39	100	268	100			

[a] Cumulative doses lagged by 2 years.
[b] Odds ratios from conditional logistic regression model.
[c] Cases and controls matched on year of birth and oblast.
[d] Confidence interval.
[e] *P* value from the 1 *df* likelihood ratio test of linear trend where the score for each category is the mean value for the cumulative dose.

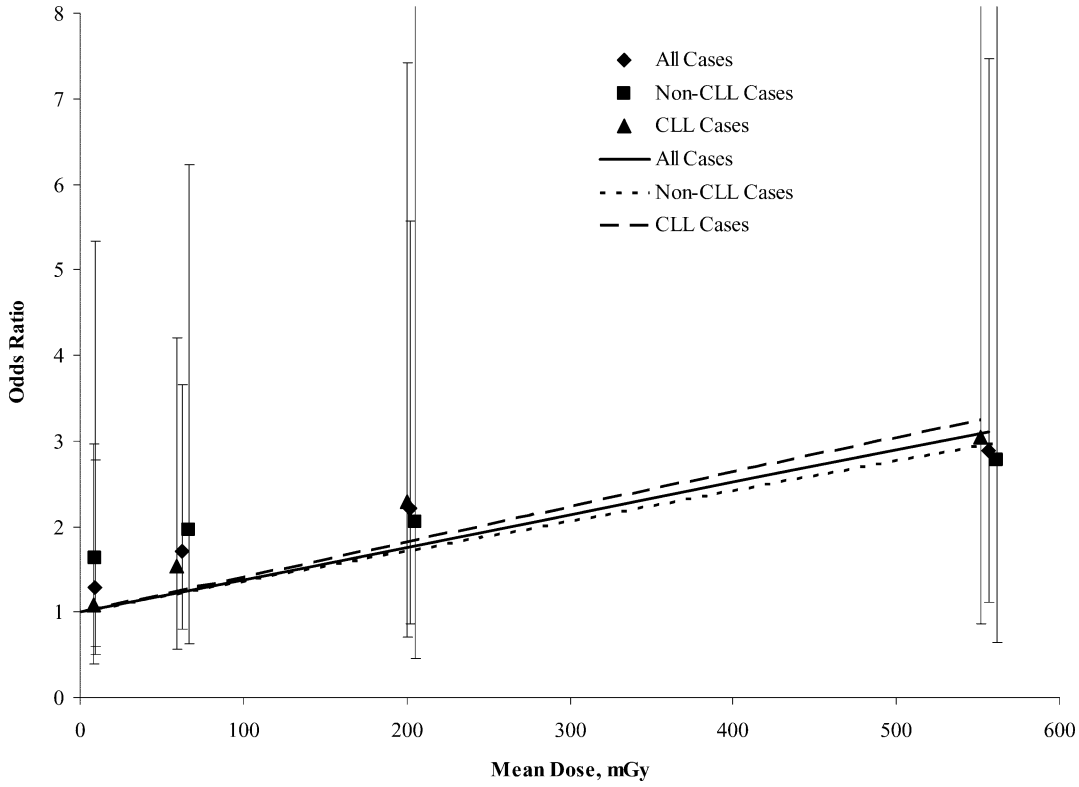

FIG. 1. Plot of the odds ratios of leukemia by mean dose for each of five dose categories and fitted dose–response lines constructed using the least-squares method.

TABLE 5
Excess Relative Risk Models of Leukemia for Dose and Interactions with Age at Exposure, Year of Diagnosis, Duration of Missions and Number of Missions

Description	*N* cases	ERR per Gy[a,b,c]	Lower 95% bound	Upper 95% bound	*P* value[d]
All cases	71	3.44	0.47	9.78	<0.01
Cell type					
Non-CLL	32	2.73	<0	13.50	0.75
CLL[e]	39	4.09	<0	14.41	
Proxy interviews					
No	29	6.20	<0	27.11	0.47
Yes	42	2.45	<0	9.46	
Age at exposure, years					
21–44	36	0.03	<0	6.03	0.07
45–63	35	8.83	1.52	32.78	
Year of diagnosis					
< 1993	19	4.67	<0	38.00	0.81
≥1993	52	3.19	0.21	10.21	
Duration of missions, months					
≤1	42	4.47	0.78	13.24	0.46
>1	29	1.92	<0	9.86	
Number of missions					
1	55	4.31	0.76	12.60	0.52
>1	16	2.03	<0	10.88	

[a] Excess relative risk per Gy.
[b] Conditional logistic regression model with cumulative doses lagged by 2 years.
[c] Cases and controls matched on year of birth and oblast.
[d] *P* value from the likelihood ratio test for interaction effects.
[e] Chronic lymphocytic leukemia.

viewed controls, we included all controls in these analyses. The ERR per Gy for directly interviewed cases was 2.5-fold that for proxy cases, although a test of interaction for source of interview data yielded a *P* value of 0.47. We did not observe a statistically significant interaction for categories of year of diagnosis, duration of missions, or number of missions. However, the ERR was nonsignificantly lower for workers with longer durations of exposure and greater numbers of missions, suggesting a reduced effect with lower dose rate. The ERR for workers first exposed before age 45 years (median age at exposure) was smaller than for those exposed at later ages ($P = 0.07$ for the likelihood ratio test for interaction effects), and a higher ERR at older ages at exposure was also seen for CLL and non-CLL cases when we analyzed them separately (not shown).

DISCUSSION

In a nested case-control study of Chornobyl cleanup workers in Ukraine, we observed a significant association between Chornobyl-related radiation dose and increased risk of total leukemia. Our risk estimate for Chornobyl cleanup workers exposed to protracted radiation was comparable to that from the Life Span Study of atomic bomb survivors exposed to high-dose-rate ionizing radiation (*3*). However, while differences were not statistically significant ($P > 0.5$), the estimates of ERR for workers exposed for longer durations or from multiple missions were about half those for workers who received their exposure within 1 month or during one mission.

The strengths of this study are many and include the relatively large number of cases and controls compared to other studies of cleanup workers, selection of cases and controls from within a large cohort of cleanup workers from Ukraine, the wide and rigorous search for diagnoses of leukemia and 99 ancillary diagnoses (diagnoses that could be misclassified and therefore mask leukemia) in all medical institutions treating leukemia in the target geographic areas, and confirmation of diagnoses for all study cases by the International Hematology Panel consisting of hematologists and hematopathologists that reviewed medical records for all cases and biological material for a majority of cases.

Furthermore, individual bone marrow doses were estimated for all study subjects by the RADRUE dosimetric method, which allows for the possibility of dose reconstruction for deceased cases and was validated in other studies (*14*). The RADRUE doses have been shown to be superior to the ''official'' doses that were found to be available for about a third of cohort members and that are subject to substantial uncertainties. Cumulative individual bone marrow radiation doses were higher than in most studies of

nuclear workers although still in the low-dose range [76.4 mGy compared to 19.4 mGy in Cardis *et al.* (*16*)].

Another strength of the study is the high interview participation rates for both cases and controls as well as for alive subjects and proxies used for deceased study subjects. To minimize potential biases, interviewers were not aware of subjects' case-control status and were carefully trained not to ask probing questions beyond those listed on the questionnaire. Similarly, doses were estimated without knowledge of subjects' case-control status and members of the International Hematology Panel did not know the radiation dose of cases under review. Finally, the information collected during interviews allowed the investigation of the effects of a number of potential confounders not generally available in other studies of cleanup workers.

A limitation of the study was that the number of cases who died and thus for whom proxy interviews were necessary was sizable. While the quality of data from the proxy interviews was more uncertain than the data collected directly from subjects, it was deemed sufficient for dose estimation based on the results of re-interviews and interviews of several coworkers for deceased cases (*14*). Uncertainties in the RADRUE dose estimates were complex; they included uncertainties in exposure-rate data and soil contamination measurements, uncertainties in the interpolation of these data in time and space, and imprecision of the data from the questionnaire. We believe that the dose uncertainties in our study were primarily classical errors and expect that they will bias risk estimates toward the null. Further analysis of dose uncertainties and their potential effects on risk estimates is planned.

While there are study limitations, the observed association between radiation and leukemia is unlikely to be due to chance given the consistency of the dose–response relationships observed in both categorical and continuous analyses, for annual and cumulative doses, and in the entire dose range as well as for doses less than 500 mGy, when adjusting for other measures of exposure at Chornobyl and for different leukemia cell subtypes. However, it must be recognized that recall bias, i.e., that cases could either preferentially recall their Chornobyl experience or else exaggerate such experiences leading to an overestimation of their dose, cannot be ruled out. The higher ERR seen for non-proxy compared with proxy cases (6.20 and 2.45 per Gy, respectively) could be an indication of recall bias or, more likely, it could reflect greater error in estimating doses for proxy cases.

We observed an increase in the risk of leukemia for workers exposed after age 45 compared to those less than 45, although the difference was not statistically significant. A similar effect has been observed in some studies of nuclear workers exposed to low-dose protracted radiation (*16*).

Most published studies of Chornobyl cleanup workers report an elevated risk of leukemia (*1, 4*), with much of the evidence coming from studies of Russian cleanup workers who received average doses of 100–200 mGy (*5–8*). Based on the dose and follow-up information for 168,000 workers from the Russian National Medical and Dosimetric Registry, Ivanov *et al.* (*5*) reported an increased risk of all leukemia with an ERR of 4.3 per Gy ($n = 48$). Risk estimation was based on a comparison of the observed incidence with the national incidence of leukemia for males from the same age groups. Two case-control studies from the same registry showed discrepant results: An initial analysis showed no significant trend with dose for all leukemia, leukemia excluding CLL, or liquidators who worked in the 30-km zone in 1986–1987 (*7*), but a later analysis estimated significant ERRs ranging from 0.28 to 15.59 per Gy for essentially the same groups (*8*). Methodological concerns prompted Boice and Holm to question the validity of this analysis (*17*). In a more recent cohort analysis of 42 cases of non-CLL among 71,870 workers from the same registry, Ivanov *et al.* (*6*) reported a significantly increased ERR of 6.7 per Gy. The reasons for the differences in estimates are not clear, but the large uncertainties in ''official'' doses from the Chornobyl Registry and absence of rigorous histopathological case verification are a concern.

Buzunov *et al.* (*9*) conducted an ecological study of leukemia occurrence among approximately 175,000 liquidators in Ukraine using data from the State Registry of Ukraine and national leukemia morbidity statistics. Leukemia incidence rates for workers first employed in 1986, when doses were relatively high, were double those for workers employed in 1987, when doses were lower.

Our findings also can be compared with those from studies of nuclear workers who were exposed to low doses of radiation at low dose rates (*16, 18*). In a pooled analysis of workers from 15 countries, approximately 400,000 nuclear workers were monitored for external radiation. Despite the large number of workers, the confidence interval for the nearly twofold ERR per Gy for leukemia excluding CLL remained wide and included unity (ERR = 1.93 per Gy, 95% CI: < 0, 8.47) (*18*). We found a similar increase in non-CLL leukemia (ERR = 2.73 per Gy, 95% CI < 0–13.50). A recent analysis of leukemia mortality in the cohort of U.S. shipyard workers exposed to protracted low-level γ radiation (*19*) also found a nonsignificant increase in risk with increasing radiation dose. Krestinina *et al.* recently reported that subjects exposed to protracted internal and external environmental ionizing radiation from radioactive discharges from the Mayak nuclear weapons complex (mean bone marrow dose = 300 mGy) had a significantly increased risk of total leukemia. The number of deaths from CLL was small, and the dose response for CLL alone was not significant (*20*).

Among males exposed to acute radiation from the atomic bombs between the ages of 20 and 60 years (similar to the present study), the ERR for non-CLL is about 3 per Gy (based on the linear term of a linear quadratic dose–response relationship) (*18*). Data on CLL are not available because CLL is very rare in Japan (*2*). Because radiation-

related leukemia risk has been shown to decrease with time since exposure, it is reasonable to predict that during the first 10–20 years of follow-up after the Chornobyl accident excess risk would be higher (approximately three- to four-fold) (*2, 21*). Thus our results for non-CLL appear to be consistent with those from the study of atomic bomb survivors.

A likely cause of the high proportion of CLL cases in our study (55%) compared with only about 40% reported by population-based cancer registries is the difference in the level of medical monitoring and diagnostic tools used (*22, 23*). Zent *et al.* (*24*) suggested that, due to the rather indolent nature of CLL, tumor registries may be missing as much as 38% of CLL compared with the incidence of CLL detected using sophisticated measures such as flow cytometric immunophenotypic analysis. Because annual medical examinations including blood tests and a visit to a hematologist are mandatory for all cleanup workers registered in the SRU (*25, 26*), it would be expected that a large number of cases would be detected that would not have been diagnosed among people receiving routine medical care. Indeed, Gluzman *et al.* (*26*) reported that 49% of total leukemia diagnosed among the Ukrainian Chernobyl cleanup workers 10–20 years after the accident were of the CLL subtype compared with only 44% in the age- and sex-comparable general population of Ukraine. The over-representation of CLL cases may also be due to the more benign clinical course and longer survival that led to a greater likelihood of ascertainment (a type of length-bias sampling) using our thorough case-finding protocol. Underascertainment of acute leukemia cases who died prior to being properly diagnosed or whose diagnoses could not be confirmed due to lack of histological materials could also have resulted in over-representation of CLL cases. However, the potential over diagnosis of CLL and under diagnosis of non-CLL cannot account for our observed positive radiation dose–response relationship for CLL since neither situation should be related to dose and because doses were estimated for similar proportions of CLL and non-CLL cases confirmed by the panel (79.6 and 84.2%, respectively, $P = 0.58$; see Table 1).

The generally similar radiation effects we found for CLL and non-CLL is somewhat surprising in view of the lack of significantly increased radiation risks for CLL observed in most other studies (*1, 16, 27, 28*). One explanation is that the higher proportion of proxies interviewed for non-CLL cases compared with CLL cases (69 and 51%, respectively, $P = 0.14$) could have resulted in less precise dose estimates for the non-CLL cases and therefore a reduction in the dose response.

Another explanation may be related to the fact that most other studies are based on mortality data. Analyzing data from atomic bomb survivors, Ron *et al.* showed that incidence data had greater diagnostic accuracy than mortality data and provided more complete information on relatively nonfatal cancers (*29*). Finch and Linet have suggested that over a quarter of all cases of CLL may be asymptomatic for many years, and even after diagnosis survival is significantly longer compared to other types of leukemia (*30*). Thus mortality data would underestimate, possibly substantially, the occurrence of CLL. Not surprisingly, recent mortality studies that evaluated dose response for CLL separately had either negative findings (*16, 31*) or positive findings with a negative dose–response trend (*19, 28, 32*). Two recent incidence-based studies of radiation workers have shown an association between CLL and occupational radiation exposure (*33, 34*), with one study (*33*) reporting a significant increase in CLL among Czech uranium miners presumably due to a γ-radiation component of exposure in the mines and the other study (*34*) reporting an elevated risk among radiologic technologists who worked during the early years, when occupational doses were presumably high. In contrast, high-dose studies of populations treated with radiotherapy for a first primary cancer showed no increase in the incidence of CLL, whereas a significant increase was demonstrated for all other types of leukemia (*35, 36*). Due to the very low CLL incidence in Japan (*2*), data on the relationship with radiation are not available from studies of atomic bomb survivors.

Some earlier genetic and molecular studies have shown that lymphatic malignancies differ from other types of leukemia, possibly explaining the apparent variation in response to radiation in the two types of leukemia (*37, 38*). However, in a recent review of the latest molecular, clinical and epidemiological evidence for radiation-associated risks of CLL, Richardson *et al.* (*39*) argue that the somatic mutations involved in CLL etiology are similar to those of other lymphatic neoplasms and that the assumption that CLL is an exception to the principles of radiation carcinogenesis is without firm foundation.

Several studies have demonstrated marked differences in the clinical course and morphological features of CLL diagnosed in Chornobyl cleanup workers and the general population (*25, 40, 41*). Chornobyl-associated CLL cases were characterized by younger age, more advanced stage of disease at presentation, and faster progression. Cleanup workers with large radiation doses had CLL characterized by high mutation rates in several genes associated with poor disease prognosis (*25, 40*). In our study, CLL cases were characterized by longer survival compared to other subtypes of leukemia (51% and 69% deceased at the time of interview, respectively).

In summary, we found a significant linear dose–response relationship between Chornobyl-related radiation exposure among Ukrainian cleanup workers and risk of total leukemia. Similar to other studies, we found an increased risk for non-CLL. Our finding of an association between CLL and ionizing radiation adds new information to the controversy regarding the effects of radiation on CLL (*41–43*). To further clarify these issues, we are extending the case-control study to ascertain cases for another 6 years (2001–2006).

IN MEMORIAM

We would like to dedicate this article to the memory of Drs. Gilbert Beebe and Geoffrey R. Howe and to acknowledge that without their tireless efforts over many years this study would not have been possible. We would also like to acknowledge Dr. Howe's contributions to the establishment of the Ukrainian Cancer Registry in the early 1990s, which will be a lasting resource for Chornobyl research studies.

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Radiation and the Risk of Chronic Lymphocytic and Other Leukemias among Chornobyl Cleanup Workers

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Background: Risks of most types of leukemia from exposure to acute high doses of ionizing radiation are well known, but risks associated with protracted exposures, as well as associations between radiation and chronic lymphocytic leukemia (CLL), are not clear.

Objectives: We estimated relative risks of CLL and non-CLL from protracted exposures to low-dose ionizing radiation.

Methods: A nested case–control study was conducted in a cohort of 110,645 Ukrainian cleanup workers of the 1986 Chornobyl nuclear power plant accident. Cases of incident leukemia diagnosed in 1986–2006 were confirmed by a panel of expert hematologists/hematopathologists. Controls were matched to cases on place of residence and year of birth. We estimated individual bone marrow radiation doses by the Realistic Analytical Dose Reconstruction with Uncertainty Estimation (RADRUE) method. We then used a conditional logistic regression model to estimate excess relative risk of leukemia per gray (ERR/Gy) of radiation dose.

Results: We found a significant linear dose response for all leukemia [137 cases, ERR/Gy = 1.26 (95% CI: 0.03, 3.58]. There were nonsignificant positive dose responses for both CLL and non-CLL (ERR/Gy = 0.76 and 1.87, respectively). In our primary analysis excluding 20 cases with direct in-person interviews < 2 years from start of chemotherapy with an anomalous finding of ERR/Gy = –0.47 (95% CI: < –0.47, 1.02), the ERR/Gy for the remaining 117 cases was 2.38 (95% CI: 0.49, 5.87). For CLL, the ERR/Gy was 2.58 (95% CI: 0.02, 8.43), and for non-CLL, ERR/Gy was 2.21 (95% CI: 0.05, 7.61). Altogether, 16% of leukemia cases (18% of CLL, 15% of non-CLL) were attributed to radiation exposure.

Conclusions: Exposure to low doses and to low dose-rates of radiation from post-Chornobyl cleanup work was associated with a significant increase in risk of leukemia, which was statistically consistent with estimates for the Japanese atomic bomb survivors. Based on the primary analysis, we conclude that CLL and non-CLL are both radiosensitive.

Key words: Chernobyl nuclear accident, Chornobyl, Ukraine, chronic lymphocytic leukemia, leukemia, matched case–control study, radiation, radiation dose–response relationship, radiation-induced leukemia. *Environ Health Perspect* 121:59–65 (2013). http://dx.doi.org/10.1289/ehp.1204996 [Online 8 November 2012]

It is well known that substantial risks of leukemia are associated with exposure to high acute doses of ionizing radiation [United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR 2008)]. Risks of leukemia associated with protracted exposures to low doses of radiation, which occur among occupationally exposed nuclear industry workers (Cardis et al. 2007; Muirhead et al. 2009) or among the general public living in areas affected by accidental releases of radioactive materials (Krestinina et al. 2010), have been reported to be of similar magnitude, but several questions remain (Jacob et al. 2009; Richardson 2009; UNSCEAR 2010). Of special concern are radiation-related leukemia risks among those who are engaged in emergency and recovery work after nuclear facility accidents because the level of exposure can be relatively high. As of 2006, over 500,000 persons from Belarus, the Russian Federation, and Ukraine had been registered as emergency and recovery workers after the 1986 Chornobyl accident (UNSCEAR 2011).

Although most types of leukemia are known to be radiogenic (Little et al. 1999; Preston et al. 1994), to date very few studies have provided substantial evidence for a radiogenic excess of chronic lymphocytic leukemia (CLL) (UNSCEAR 2008). However, the view that CLL is not caused by radiation has been questioned (Linet et al. 2007; Richardson et al. 2005), and more recent studies based on incident rather than mortality outcomes have suggested a radiation effect on CLL as well as on other types of leukemia (Kesminiene et al. 2008; Lane et al. 2010; Mohner et al. 2010; Rericha et al. 2006; Romanenko et al. 2008b).

In our previous study of leukemia occurring between 1986 and 2000 among Chornobyl cleanup workers from Ukraine (Romanenko et al. 2008b), we found a significantly increased risk of leukemia, similar in magnitude to the estimate from the Japanese atomic bomb survivors (UNSCEAR 2008). The data indicated elevated risks for both CLL and other leukemias. We therefore extended the study through 2006, with a near doubling of the number of leukemia cases. We herein report results of the analysis of the extended data.

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Methods

Study data. Data were from a nested case–control study in a cohort of 110,645 male Ukrainian workers who were 20–60 years of age during cleanup activities in 1986–1990 after the Chornobyl nuclear power plant accident and who were registered in the Chornobyl State Registry of Ukraine (SRU) before 1992 and resided in Kyiv City or in any one of five study oblasts (areas similar to a state or province: Cherkasy, Chernihiv, Dnipropetrovsk, Kharkiv, and Kyiv) at the time of registration (Romanenko et al. 2008a).

Potential cases for the period of 1986–2000 were identified among persons diagnosed with leukemia or with a diagnosis from a broad screening list of 99 ancillary conditions that might possibly represent cases of leukemia (including myelodysplasia, non-Hodgkin lymphoma, and multiple myeloma) at all health care institutions in the study area; potential cases were then used to create a Provisional Leukemia Registry (Romanenko et al. 2008a). Potential cases during 2001–2006 were identified by linkage of the SRU cohort with the Ukrainian Cancer Registry (UCR), which achieved nationwide coverage in 1997 (Fedorenko et al. 2011).

A total of 162 cases of leukemia were confirmed by the International Hematology Panel of five hematologists/hematopathologists. Most cases were confirmed unanimously after initial review of the cytological material and medical records or, lacking such initial unanimity, by a mutually acceptable consensus diagnosis after reexamination of all materials and in-depth discussion between the panel members. Descriptions of the clinical courses and histological confirmation of the diagnoses from the medical records were available for all cases. Bone marrow aspirates/biopsy slides and/or peripheral blood smears were available for 113 cases (70%). Acute leukemia types were classified using the World Health Organization system of classification (Jaffe et al. 2001). CLL diagnoses were based on the criteria established by the U.S. National Cancer Institute (NCI) Working Group (Cheson et al. 1996). The diagnostic confirmation rate for CLL (89%) and non-CLL cases (79%) did not differ significantly ($p = 0.103$).

With a targeted 5:1 control:case ratio, we used incidence–density sampling to randomly select 5–9 controls for each potential case from members of the cohort who were alive and at risk at the time of the case diagnosis and were matched to the case on place of residence (in one of five oblasts or Kyiv City) and year of birth, regardless of whether the potential control was alive at the time of ascertainment. Among 1,364 selected controls, 901 were interviewed, 215 refused to participate, 213 could not be traced, and 35 moved out of the study regions. Response rates, including untraceable subjects, were 70% for live controls, 49% for next-of-kin, and 64% for colleagues responding for deceased controls. There were 677 controls interviewed for 137 confirmed and interviewed leukemia cases. In addition, 224 controls were interviewed for cases that were not subsequently interviewed (directly or by proxy) or not confirmed. We rematched 186 of the latter controls to confirmed cases using the matching criteria, resulting in a total of 863 controls. We used all 863 controls in the analyses because results with and without the extra controls were similar (data not shown).

A time-and-motion dose reconstruction method, known as Realistic Analytical Dose Reconstruction with Uncertainty Estimation (RADRUE), was developed specifically for this study and for a similar study conducted in Belarus, Russia, and Baltic countries (Kesminiene et al. 2008) by an international group of scientists including experts from Belarus, France, Russia, the United States, and Ukraine (Chumak et al. 2008; Kryuchkov et al. 2009). The method used combined data on work history from dosimetric questionnaires with field radioactivity measurements to estimate individual bone marrow doses for all study subjects. In-person interviews were conducted by trained interviewers and included questions concerning locations of work and residence while in the 30-km exclusion zone around the Chornobyl nuclear power plant, types of work, transportation routes, and corresponding dates. For deceased cases or controls, proxy interviews were conducted with next-of-kin for demographic and medical information and with co-workers for work histories in the 30-km exclusion zone. Proxy interviews were conducted for 69 deceased cases (38 non-CLL and 31 CLL, 50% of all cases) and 43 deceased controls (5% of all controls).

Radiation dose estimates were not available for 25 cases (15%): 2 were ineligible, 17 could not be traced, 4 refused to complete the dosimetry questionnaire, and 2 had poor quality of interview response. Response rates were 96% for live cases and 79% for next-of-kin and colleagues responding for deceased cases. The present study thus included 137 confirmed cases with radiation dose estimates, 79 CLL and 58 non-CLL cases [6 with acute lymphocytic leukemia, 16 with acute myeloid leukemia, 7 with acute leukemia/not otherwise specified, 24 chronic myeloid leukemia, and 5 with other chronic leukemia (2 large granular lymphocyte leukemia–natural killer cell type, and 3 large granular lymphocyte leukemia–T-cell type)].

The protocol for the study was approved by the institutional review boards of the NCI (Bethesda, MD, USA); the University of California, San Francisco, School of Medicine (San Francisco, CA, USA); and the National Research Center for Radiation Medicine (Kyiv, Ukraine). All participants gave written informed consent.

Statistical analysis. As in our previous study (Romanenko et al. 2008b), we fitted a conditional logistic regression model that assumed a linear dose–response relationship although we evaluated several alternative forms, including linear–quadratic, exponential, and power models. The model was fitted by maximum likelihood (McCullagh and Nelder 1989) using the EPICURE statistical package (Preston et al. 1993). The excess relative risk per gray (ERR/Gy) computed by this model is an estimate of the excess risk associated with exposure to 1 Gy relative to no radiation exposure. We also estimated relative risks (RRs) for radiation dose categories. Using likelihood ratio tests, we examined the potential modifications of association between radiation and the disease outcomes by means of interaction terms between radiation dose (continuous) and indicator terms for categorical variables (leukemia subtype, proxy status, 0–1 vs. 2–15 years from start of chemotherapy to direct interview, and type of work performed in the 30-km Chornobyl zone) or continuous variables (year of case diagnosis, time since first exposure, and age at first exposure), although for ease of presentation, the ERR/Gy estimates are shown for categories of continuous variables. The population-attributable risks (PARs) of all leukemia, CLL, and non-CLL were estimated as the reduction in the leukemia risk after elimination of radiation exposure as a fraction of the total leukemia risk:

$$\mathrm{PAR} = \sum_k \mathrm{P}_k \times (\mathrm{RR}_k - 1)/\sum_k \mathrm{P}_k \times \mathrm{RR}_k, \quad [1]$$

where $k = 0, 1, \ldots, 100$, and P_k and RR_k are the proportion and model-based estimates of RR at the kth percentile dose level. For these computations, we approximated the bone marrow dose distribution by using percentiles. Confidence limits for PAR were based on the substitution method (Daly 1998).

Our analyses were based on the cumulative doses derived as the sums of the arithmetic means of the annual 1986–1990 bone marrow doses estimated by generating 10,000 realizations of dose predictions from the RADRUE method (Chumak et al. 2008). We assessed lag interval, a period of recent exposure assumed unrelated to disease, for the calculation of cumulative dose from 1986 to 1990 in 1-year increments between 0 and 10 years. The deviance, a measure of model fit, was minimized for both CLL and non-CLL analyses when we set the lag interval to either 1 or 2 years [see Supplemental Material, Table S1 (http://dx.doi.org/10.1289/ehp.1204996)], although the deviances were very similar for up to a lag of 5 years. When 20 cases who were interviewed < 2 years from start of chemotherapy were excluded, the optimal lag both

for CLL and non-CLL was 2 years. Choice of lag had little effect on the risk estimates (results not shown). Since various other bodies (Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation 2006; UNSCEAR 2008) recommend a lag of 2 years for non-CLL, we lagged radiation doses by 2 years in all analyses.

Tests of all hypotheses were based on likelihood ratio tests. All tests were two-sided with a specified type I error of 0.05 and confidence intervals (CIs) for risk estimates were derived by the profile likelihood method (McCullagh and Nelder 1989). If the likelihood being sought for a lower bound estimate did not converge, it was given by $< -1/D_{max}$, where D_{max} was the maximum radiation dose.

Results

The age at diagnosis of 137 cases ranged from 25 to 78 years (median, 56) and the corresponding age for 863 controls ranged from 25 to 79 years (median, 55). Mean ± SD estimated bone marrow radiation doses for cases and controls were 132.3 ± 342.6 mGy and 81.8 ± 193.7 mGy, respectively (Table 1). Seventy-eight percent of study participants had bone marrow doses < 100 mGy, and 87% < 200 mGy. Cases and controls did not differ significantly by urban versus rural residential status at the time of interview, age at first radiation exposure in the 30-km Chornobyl zone, or education; however, more cases than controls were proxy-interviewed ($p < 0.001$) (Table 1). Cases and controls did not differ significantly by calendar year of first cleanup mission, type of work or total number of missions, or by self-reported smoking, alcohol consumption, medical or diagnostic radiation exposures, or occupational exposures to chemicals or radiation before and after the Chornobyl accident (results not shown). Thirty-eight percent of cleanup workers were in the 30-km zone around the Chornobyl nuclear power plant for > 2 months (median time in the zone for all workers, 35 days; range, 1–1,711 days; similar for cases and controls, p Wilcoxon = 0.729).

For all leukemias, we found a significant positive association with continuous radiation dose with an estimated ERR/Gy = 1.26 (95% CI: 0.03, 3.58, $p = 0.041$) (Table 2). However, preliminary analysis identified a significant ($p = 0.021$) difference in the dose response for 20 cases (6 non-CLL and 14 CLL) with direct in-person interviews < 2 years from start of chemotherapy compared with other cases [ERR/Gy = –0.47 (95% CI: < –0.47, 1.02, $p = 0.244$) for 20 cases vs. ERR/Gy = 2.38 (95% CI: 0.49, 5.87, $p = 0.004$) for the remaining 117 cases] [Table 2 and also see Supplemental Material, Table S2, (http://dx.doi.org/10.1289/ehp.1204996)]. Because of this marked disparity, we limited our primary analyses to cases who were interviewed

Table 1. Descriptive characteristics [*n* (%)] of cases and controls identified during follow-up (1986–2006).

Characteristic	Cases ($n = 137$)	Controls ($n = 863$)	p-Value[a]
Radiation dose, mGy [mean ± SD (range)][b]	132.3 ± 342.6 (0–3220.0)	81.8 ± 193.7 (0–2600.0)	0.119[c]
Year of birth			0.988
1923–1929	10 (7)	67 (8)	
1930–1939	38 (28)	222 (26)	
1940–1949	43 (31)	285 (33)	
1950–1959	37 (27)	234 (27)	
1960–1965	9 (7)	55 (6)	
Areas of study			0.938
Cherkasy Oblast	7 (5)	60 (7)	
Chernihiv Oblast	11 (8)	77 (9)	
Dnipropetrovsk Oblast	26 (19)	155 (18)	
Kharkiv Oblast	17 (12)	107 (12)	
Kyiv Oblast	27 (20)	183 (21)	
Kyiv City	49 (36)	281 (33)	
Type of residence at time of interview			0.090
Urban	101 (74)	680 (79)	
Rural	19 (14)	151 (18)	
Other	10 (7)	32 (4)	
Unknown	7 (5)	0 (0)	
Age at first exposure (years)			0.970
20–34	31 (23)	207 (24)	
35–41	36 (26)	221 (26)	
42–49	40 (29)	239 (28)	
50–63	30 (22)	196 (23)	
Education			0.474
≤ 8 years	16 (12)	131 (15)	
High school	46 (34)	341 (40)	
Trade school	34 (25)	200 (23)	
College	34 (25)	188 (22)	
Unknown	7 (5)	3 (0)	
Proxy interviews			< 0.001
No	68 (50)	820 (95)	
Yes	69 (50)	43 (5)	

[a]p-Value from the chi-square test unless otherwise stated. [b]Bone marrow radiation dose lagged by 2 years. [c]p-Value from the Wilcoxon rank sum test.

Table 2. ERR/Gy (95% CIs) for leukemia within categories of various factors.

Model description	Cases (*n*)	ERR/Gy (95% CI)	p-Value[a]	p Interaction[b]
All cases	137	1.26 (0.03, 3.58)	0.041	
Excluding cases with direct interviews < 2 years from start of chemotherapy	117	2.38 (0.49, 5.87)	0.004	
Leukemia subtype				
Non-CLL	52	2.21 (0.05, 7.61)	0.039	0.888
CLL	65	2.58 (0.02, 8.43)	0.047	
Proxy status[c]				
Proxy	69	3.98 (< –0.15, 25.23)		0.420
Direct interview	48	0.88 (< –0.38, 5.28)		
Year of case diagnosis				
1986–1994	33	6.70 (0.27, 27.10)		0.141[d]
1995–2000	36	2.69 (–0.04, 11.23)		
2001–2006	48	1.25 (< –0.69, 5.35)		
Type of work performed in the 30-km Chornobyl zone				
Early responders	32	1.49 (–0.02, 5.07)		0.711
Military personnel	43	4.23 (0.12, 12.59)		
Professional nuclear power workers	5	2.72 (< –0.91, 19.58)		
Other	37	4.23 (–0.27, 15.25)		
Time since first exposure (years)				
≤ 9	38	5.10 (–0.02, 19.17)		0.162[d]
10–14	34	4.09 (0.39, 13.47)		
15–20	45	0.84 (< –0.78, 4.50)		
Age at first exposure (years)				
20–34	27	1.01 (< –0.98, 8.65)		0.249[d]
35–41	30	1.61 (–0.49, 8.80)		
42–49	33	5.67 (0.58, 21.79)		
50–63	27	2.00 (< –0.38, 10.11)		

Cases with direct interviews < 2 years from start of chemotherapy are excluded from all analyses except the "all cases" analysis.
[a]p-Value of departure of ERR/Gy from zero. [b]p-Value for interaction effects. [c]Background rate adjusted for proxy status. [d]p-Value from the linear trend test.

2–15 years after start of chemotherapy, did not have chemotherapy, or for whom proxy interviews were used and their matched controls (85% of all cases and 83% of all controls).

RRs increased with increasing radiation dose for all leukemia (Figure 1). Tests for quadratic, exponential, or power deviations from the linear dose response shown in Figure 1 were not significant (p = 0.927, p = 0.917, p = 0.267, respectively). The dose responses increased significantly for both non-CLL [ERR/Gy = 2.21 (95% CI: 0.05, 7.61, p = 0.039)] and CLL [ERR/Gy = 2.58 (95% CI: 0.02, 8.43, p = 0.047)] subtypes, with tests for interaction consistent with homogeneity (p = 0.888)] (Table 2).

We found no significant difference in ERR/Gy estimates by proxy or direct interviews (p = 0.420), calendar period of diagnosis (p = 0.141), or type of work performed in the 30-km Chornobyl zone (p = 0.711) (Table 2). Although also not significant, ERR/Gy estimates tended to decrease with increasing time (years) from first radiation exposure in the Chornobyl zone and to increase with increasing age at first exposure (p = 0.162, p = 0.249, respectively) (Table 2). The proportion of proxy versus direct interviews decreased over time (60.0%, 73.9%, 55.6%, and 54.2% for cases diagnosed in 1986–1989, 1990–1994, 1995–2000, and 2001–2006, respectively).

We estimated that approximately 16% of all leukemia cases in our Chornobyl cleanup worker population over a period of 20 years of follow-up [PAR = 16.4% (95% CI: 3.9, 32.6)] were attributable to radiation exposure from the Chornobyl accident. The majority of the PAR arose from dose groups of < 200 mGy in which there were large numbers of cleanup workers (Figure 2). Proportions of CLL and non-CLL cases attributable to radiation were similar, with PARs of 17.5% (95% CI: 0.2, 41.0) and 15.4% (95% CI: 0.4, 38.5), respectively.

For completeness, we evaluated modifications of the ERR/Gy presented in Table 2 using all case and control data [see Supplemental Material, Table S2 (http://dx.doi.org/10.1289/ehp.1204996)]. In general, results using the full dataset were consistent with the primary analysis. However, the ERR/Gy for CLL [0.76 (95% CI: < –0.38, 3.84, p = 0.352)] was lower than the estimated ERR/Gy for CLL from our primary analysis excluding 14 CLL cases [2.58, (95% CI: 0.02, 8.43, p = 0.047)]. In the analysis using the full dataset, as in the primary analysis, the ERRs were not significantly different between CLL and non-CLL outcomes (p = 0.536).

Discussion

Here we report several important findings concerning the late effects of ionizing radiation exposure. First, our results confirm and significantly strengthen the evidence from our previous study (Romanenko et al. 2008b) that showed significant associations between protracted radiation exposure at low doses and leukemia incidence. Increased risks of leukemia, although not statistically significant, were also reported from a study of Chornobyl cleanup workers from Belarus, Russia, and Baltic countries (Kesminiene et al. 2008). Second, our results indicate that radiation risk estimates are elevated for both CLL and non-CLL. Generally, assessment of radiation risks of cancer and leukemia from exposures to low or protracted radiation doses derives from extrapolation of risks from epidemiological studies of populations exposed to single or high doses (e.g., studies of Japanese atomic bomb survivors and of medically exposed persons) (UNSCEAR 2008). It has been assumed that protraction of radiation dose results in a reduction of adverse biological effects, and an important uncertainty involved in these extrapolations relates to the risk associated with acute versus protracted exposure. The mean cumulative radiation doses (0.092 Gy) received by the Chornobyl cleanup workers were lower than reported for the atomic bomb survivors (0.24 Gy) (UNSCEAR 2008), and the ERR/Gy estimate of 2.21 (95% CI: 0.05, 7.61) for non-CLL was lower than the ERR/Gy of 3.98 (90% CI: 2.32, 6.45) for exposure at ≥ 40 years of age that can be estimated from the atomic bomb survivor data, although the estimates are comparable given the range of statistical uncertainty.

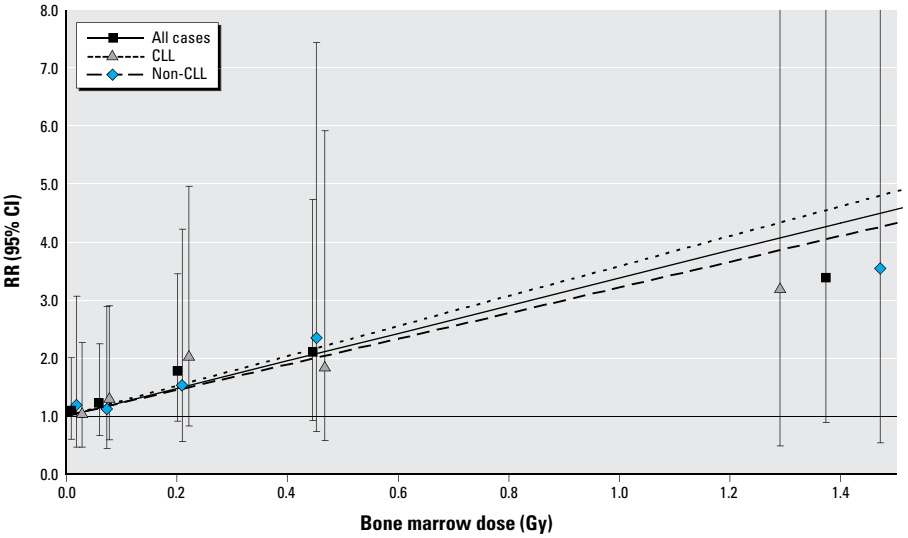

Figure 1. RRs (95% CIs) of leukemia by categories of radiation dose and fitted linear dose–response models. For display purposes, we added offsets to category mean doses on the abscissa coordinate to separate the overlapping estimates (10 mGy for non-CLL and 20 mGy for CLL analyses, respectively).

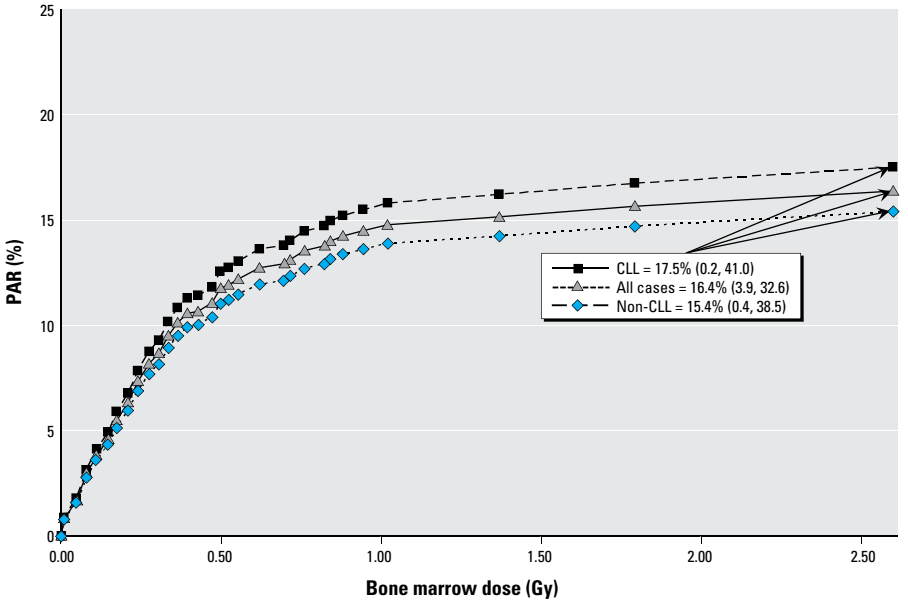

Figure 2. PARs of all leukemia and CLL and non-CLL, separately.

Chornobyl cleanup workers had higher radiation doses than those reported in other studies of incident leukemia after protracted radiation exposures, for example, the United Kingdom (mean = 0.025 Gy; Muirhead et al. 2009) or Canadian (0.007 Sv; Sont et al. 2001) radiation workers, Eldorado (0.052 Sv; Lane et al. 2010) or East German (0.024 Gy; Mohner et al. 2010) uranium miners, and the RRs of non-CLL leukemia were generally comparable [ERR/Gy = 1.78 (90% CI: 0.17, 4.36) for UK and ERR/Gy = 2.7 (90% CI: < 0, 18.8) for Canadian radiation workers]. Radiation-related risks of incident leukemia in the cohort of Techa River residents exposed to radioactive releases from the Mayak nuclear facility were higher but statistically comparable to the risks estimated in our study [ERR/Gy = 4.9 (95% CI: 1.6, 14.3) (Krestinina et al. 2010)], possibly related to the fact that 92% of their bone marrow dose (mean = 0.30 Gy) was due to internal exposures to strontium.

We estimated similar radiation-related risks for CLL and non-CLL in our primary analysis after excluding a subset of cases with interviews < 2 years from start of chemotherapy. The associations were attenuated when all cases were included in the analysis, particularly for CLL, but the ERRs for CLL and non-CLL were not significantly different in either analysis. The majority of epidemiological studies of radiation-exposed populations, whether from occupational or environmental exposures (Cardis et al. 2007; UNSCEAR 2008), or from therapeutic exposures (Boice et al. 1987; Curtis et al. 1994; Damber et al. 1995) have reported no excess of CLL. In reviewing the epidemiology and etiology of CLL, Linet et al. (2007) and Richardson et al. (2005) stressed the need for special care to ascertain CLL cases, especially when relying on information from death certificates, because of the dormant characteristics of this type of leukemia. It is thus pertinent that the recently emerging evidence of a radiogenic etiology for CLL derives mainly from incidence studies. In particular, indications for increased risks of CLL from radiation exposure have come from incidence studies of Chornobyl cleanup workers from Belarus, Russia, and Baltic countries (Kesminiene et al. 2008), and from uranium miners with exposures to alpha particles and gamma radiation in Canada, Germany, and Czechoslovakia (Lane et al. 2010; Mohner et al. 2010; Rericha et al. 2006). On the other hand, radiation and CLL were not associated according to analyses of incidence data in UK radiation workers (Muirhead et al. 2009) or the Techa River residents (Krestinina et al. 2010). The inconsistent results from studies of various exposed groups are puzzling, possibly implying diagnostic variability between the studies, and indicate the need for more intensive investigations in these and other irradiated populations.

While B cell–derived CLL may differ from other types of leukemia in etiology and pathogenesis, there is biological plausibility for the radiogenic potential for CLL. Mature B-cell CLLs are clonal proliferations of B cells at various stages of differentiation, and the initiating genetic lesions can occur in immature bone marrow B cells (Chiorazzi et al. 2005). Recent studies reported marked similarities in somatic mutations of CLL and other leukemias (Richardson et al. 2005). Also, it is possible that radiation may trigger the progression of benign monoclonal B-cell lymphocytosis, a putative precursor to CLL (Linet et al. 2007).

The strengths of this study include the large number of cases compared to studies of high- and moderate-dose exposures and of low-dose exposures among occupationally exposed workers, the selection of cases and controls from within a large cohort of cleanup workers of the 1986 Chornobyl nuclear power plant accident from Ukraine, the wide and rigorous search for diagnoses of leukemia, and the confirmation of all diagnoses by a panel of hematologists and hematopathologists based on medical records that were available for all cases, and biological materials (including bone marrow aspirates/biopsy slides and/or peripheral blood smears) that were available for 113 cases (70%). In particular, the diagnostic confirmation rates for CLL (89%) and non-CLL cases (79%) were high and comparable. In a study of cleanup workers from Belarus, Russia, and Baltic countries (Kesminiene et al. 2008), slides and case notes were available for review for 73% of cases, but 15% of the material submitted for review was judged to be inadequate for diagnosis. The interview participation rates in our study for both cases and controls as well as for alive subjects and proxies for deceased study subjects were reasonable. To minimize potential biases, interviewers were not aware of case–control status and were carefully trained not to ask probing questions beyond those listed on the questionnaire. Similarly, doses were estimated without knowledge of case–control status and members of the hematology panel did not know the radiation dose of cases under review. Finally, the information collected during interviews allowed us to estimate the effects of a number of potential confounders not generally available in other studies of cleanup workers (Ivanov 2007).

As in many retrospective case–control studies, recall bias can lead to biased estimation of radiation doses and is a concern in the present study. However, repeat interviews of alive subjects suggested good recall of missions within the Chornobyl cleanup zone (Kryuchkov et al. 2009). Fifty percent of case information was provided by proxy interviews. Mean bone marrow doses for subjects with direct and proxy interviews were not significantly different (p Wilcoxon = 0.577 and 0.512 for cases and controls, respectively). ERR/Gy estimates were higher, although not significantly so (p = 0.420), for proxy-interviewed than directly-interviewed subjects. Cleanup workers generally worked in groups and performed similar work, with co-worker proxies having first-hand knowledge about cleanup activities of deceased workers. Comparison of data from proxy interviews of live subjects with that from the subjects themselves resulted in comparable radiation dose estimates averaged over 102 pairs of subjects and proxies (geometric mean of the ratio of doses = 0.91), but large variabilities were suggested when ratios of doses for individual pairs of subjects and proxies were considered (Kryuchkov et al. 2009). Participation rates were higher for alive cases than for alive controls. Kesminiene et al. (2008) reported generally similar findings, with participation rates for cases also tending to be somewhat greater than for controls at 97% and 96%, respectively, for cleanup workers from Belarus; 87% and 91%, respectively, from Russia; and 82% and 73%, respectively, from Baltic countries.

Case ascertainment procedures varied during the study period of 1986–2006. As noted in the "Methods," we identified cases using local health care facilities before 2001, whereas later cases were identified through the linkage of the cohort file with the UCR files. We compared ascertainment methods by using both procedures in Kyiv City. Case identification was identical, except for one recently diagnosed case that would have been reported to the UCR later in the year. In addition, we searched UCR files for cases diagnosed in 1986–2000 in areas other than study areas and did not identify any new cases among cohort members.

We observed a significant increase in the risk of leukemia with radiation dose based on the entire study sample. However, a preliminary examination of differences in various characteristics of participating cases, ascertained using the two methods described above, indicated that cases with direct in-person interviews < 2 years from start of chemotherapy treatment had mean bone marrow radiation dose estimates significantly lower than other cases interviewed in-person (16.8 vs. 121.4 mGy, 7-fold difference in means, p Wilcoxon = 0.036), and these doses were uniformly lower across all types of work performed in the 30-km zone, whereas the mean doses for controls from both groups were almost identical. The ERR/Gy estimates for cases with direct interviews < 2 years from start of chemotherapy (ERR/Gy = –0.47) and the remaining cases (ERR/Gy = 2.38) differed significantly (p = 0.021), with the former estimate incompatible with our current understanding of radiation-related leukemia risk. ERR/Gy estimates in the former group were negative overall and by time since first

exposure, for cases diagnosed in 1986–2000 and 2001–2006, and for CLL and non-CLL cases (data not shown). The discrepancy could have arisen by chance or from an unknown ascertainment anomaly. Other possible reasons were that the 20 cases were undergoing therapy at the time of interview or were in poorer health compared to other cases, which could have influenced the accuracy of recall. In our primary analyses, we omitted these 20 cases so that results were not unduly influenced. Nevertheless, patterns of results using all cases were generally similar. In the analysis using all cases, the risks both for CLL and non-CLL were lower, particularly for CLL [0.76 (95% CI: < –0.38, 3.84, p = 0.352) vs. 2.58 (95% CI: 0.02, 8.43, p = 0.047)] [Table 2 and also see Supplemental Material, Table S2 (http://dx.doi.org/10.1289/ehp.1204996)]. In other respects, in relation to the variation of risks by year of case diagnosis, type of work performed, time since first exposure, or age at first exposure, the patterns were broadly similar (see Supplemental Material, Table S2). However, it must be recognized that our final results derived from a post hoc subgroup analysis.

The mean radiation doses for cases ascertained in 1986–2000 (Romanenko et al. 2008b) and 2001–2006 after excluding cases with direct in-person interviews < 2 years from start of chemotherapy treatment, were similar (mean ± SD) (143.8 ± 408.8 mGy and 152.0 ± 286.8, respectively, p Wilcoxon = 0.616), and there was no statistically significant difference in the dose response [ERR/Gy = 3.44 (95% CI: 0.47, 9.78) vs. ERR/Gy = 1.25 (95% CI: < –0.69, 5.35), p for interaction = 0.403, not shown]. Tests of linear trend for modifying effects of calendar year of diagnosis and years since first exposure were not statistically significant (p = 0.141 and p = 0.162, respectively, Table 2), but estimated radiation-related RRs of all leukemia generally tended to decrease. The decreasing temporal trend may have, at least partially, been due to the higher ERR/Gy associated with proxy interviews, which were conducted with many of the leukemia cases diagnosed in the early years after the accident.

The proportion of CLL cases in our study (58%) was higher than the approximately 40% reported by most population-based cancer registries (Dores et al. 2007) and 44% of all diagnosed leukemias among males in Ukraine (Gluzman et al. 2006). [Note that this number differs from the 29.32% reported in Gluzman et al. (2006), which was calculated as a proportion of CLL among all hematological malignancies, including multiple myeloma and NHL.] An earlier study suggested that cancer registries may be missing as much as 38% of CLL compared with the incidence of CLL detected using sophisticated measures such as flow cytometric immunophenotypic analysis (Zent et al. 2001). Using the age-specific incidence rate of CLL among men in Ukraine for 2003, we estimated that the number of CLL cases diagnosed in our cohort of 110,645 male cleanup workers over the period of 20 years after the accident was 60% higher than what would be expected for the general male population of Ukraine [standardized incidence ratio = 1.60 (95% CI: 1.3, 2.0)]. Although part of this increase could be due to estimated radiation effects of CLL, we speculate that performance of recommended annual medical examinations, including blood tests and a visit to a hematologist, for Chornobyl cleanup workers could have resulted in better case ascertainment and/or detection of cases at earlier stages than in a general population (Gluzman et al. 2006).

Conclusions

Our findings provide important evidence of increased risk of leukemia associated with chronic protracted exposure to low doses of ionizing radiation. The finding from our primary analysis of similar radiogenic risks both for CLL and non-CLL was based on a well-defined population-based cohort, rigorous case ascertainment, and expert hematological review coupled with well-characterized radiation dose estimates. In our cohort of cleanup workers from 1986 through 2006, about 16% (19 cases) of all leukemia were attributed to radiation exposure, with similar estimates for non-CLL (15%) and CLL (18%). CLL is the most common type of leukemia in this cleanup worker population and, as the workers age, CLL cases will rapidly increase, raising concerns for medical consequences. The radiogenic risk for CLL also has important public health implications in other populations because it is the most prevalent type of leukemia in Western populations, with approximately 16,000 cases estimated to be diagnosed in the United States in 2012 (Howlader et al. 2012). Further investigations are needed to develop a better understanding of the association between radiation and CLL.

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Supplemental Material

Radiation and the Risk of Chronic Lymphocytic and Other Leukemias among Chornobyl Cleanup Workers

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Supplemental Material, Table S1: Comparison of deviances from analyses using various lag times.

	Latent period (years)					
	1	**2**	**3**	**4**	**5**	**10**
All cases without exclusions (n=137)						
All cases	525.5	525.6	526.0	526.2	526.0	527.9
CLL	301.4	301.4	301.6	301.8	301.8	302.3
non-CLL	223.6	223.8	223.9	223.7	223.3	223.5
Excluding cases with direct interviews less than 2 years from start of chemotherapy (n=117)						
All cases	440.3	440.5	441.1	441.5	441.0	443.9
CLL	243.1	243.1	243.7	244.2	244.2	246.4
non-CLL	197.1	196.7	197.5	197.3	196.8	196.9

Supplemental Material, Table S2: Excess relative risk per Gy (ERR/Gy) with 95% confidence interval (CI) for leukemia within categories of various factors. In contrast to Table 2, cases with direct interviews less than 2 years from start of chemotherapy are included.

Model Description	N cases	ERR/Gy (95% CI)	*P* value[a]	*P* interaction[b]
All cases	137	1.26 (0.03, 3.58)	0.041	
Leukemia subtype				
non-CLL	58	1.87 (-0.02, 6.54)	0.055	0.536
CLL	79	0.76 (<-0.38, 3.84)	0.352	
Proxy status[c]				
Proxy	69	5.10 (<-0.81, 29.29)		0.098
Direct interview	68	-0.10 (<-0.38, 1.74)		
0-1 years from start of chemotherapy	20	-0.47 (<-0.47, 1.02)	0.244	0.103
2-15 years from start of chemotherapy	48	1.45 (<-0.74, 7.62)	0.254	
Year of case diagnosis				
1986-1994	33	6.70 (0.27, 27.10)		0.040[d]
1995-2000	40	2.11 (-0.11, 8.87)		
2001-2006	64	0.26 (<-0.47, 2.47)		
Type of work performed in the 30-km Chornobyl zone				
Early responders	36	0.74 (-0.18, 3.01)		0.682
Military personnel	49	3.38 (-0.19, 10.54)		
Professional nuclear power workers	5	1.75 (<-0.54, 15.95)		
Other	47	2.02 (-0.69, 9.42)		
Time since first exposure, years				
0-9	38	5.02 (-0.04, 18.85)		0.048[d]
10-14	38	3.24 (0.20, 10.74)		
15-21	61	0.06 (<-0.47, 2.00)		
Age at first exposure, years				
20-34	31	0.43 (<-0.98, 6.24)		0.105[d]
35-41	36	0.58 (-0.58, 4.85)		
42-49	40	2.20 (-0.09, 9.84)		
50-63	30	1.87 (<-0.38, 9.49)		

[a] *P* value of departure of ERR/Gy from zero.

[b] *P* value for interaction effects.

[c] Background rate adjusted for proxy status.

[d] *P* value from the linear trend test.

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Non-Radiation Risk Factors for Leukemia: A case-control study among Chornobyl Cleanup Workers in Ukraine

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Abstract

Background—Occupational and environmental exposure to chemicals such as benzene has been linked to increased risk of leukemia. Cigarette smoking and alcohol consumption have also been found to affect leukemia risk. Previous analyses in a large cohort of Chornobyl clean-up workers in Ukraine found significant radiation-related increased risk for all leukemia types. We investigated the potential for additional effects of occupational and lifestyle factors on leukemia risk in this radiation-exposed cohort.

Methods—In a case-control study of chronic lymphocytic and other leukemias among Chornobyl cleanup workers, we collected data on a range of non-radiation exposures. We evaluated these other potential risk factors in analyses adjusting for estimated bone marrow radiation dose. We

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Competing Interests:
The authors declare they have no competing interests.

Authors' Contributions:
Drs. Gudzenko, Bazyka, Zablotska, Hatch and Mabuchi contributed to the design and conception of the study.
Drs. Gudzenko, Hatch, Brenner, and Zablotska contributed to analysis and interpretation of the data.
Drs. Dyagil, Chumak and Reiss contributed specialized expertise.
Drs. Gudzenko and Hatch drafted the manuscript.
Drs. Bazyka, Mabuchi, Reiss, and Zablotska helped revise the manuscript critically.
Dr. Babkina was responsible for acquisition of the data.

calculated Odds Ratios and 95% Confidence Intervals in relation to lifestyle factors and occupational hazards.

Results—After adjusting for radiation, we found no clear association of leukemia risk with smoking or alcohol but identified a two-fold elevated risk for non-CLL leukemia with occupational exposure to petroleum (OR=2.28; 95% Confidence Interval 1.13, 6.79). Risks were particularly high for myeloid leukemias. No associations with risk factors other than radiation were found for chronic lymphocytic leukemia.

Conclusions—These data – the first from a working population in Ukraine – add to evidence from several previous reports of excess leukemia morbidity in groups exposed environmentally or occupationally to petroleum or its products.

Keywords

leukemia; Ukraine; Chornobyl cleanup workers; petroleum; benzene

1. Introduction

Leukemia as an early and late health effect of exposure to ionizing radiation has long been recognized (UNSCEAR 2008; Preston et al., 1994; Little MP, 2008; Ron E, 2003; Vrijheid et al., 2008; Kesminiene et al., 2008; Hsu et al., 2013; Pearce et al., 2012; Matthews et al., 2013). In addition to ionizing radiation, occupational and environmental exposure to certain chemicals, principally benzene, has also been found to increase the risk of leukemia (Polychronakis et al. 2013; Vlaanderen et al., 2011; Infante PF, 2013). Benzene as a single compound, or as part of a mixture of solvents, has most often been linked to acute myeloid leukemia (AML). However, some studies suggest it may be related to other subtypes as well, including chronic lymphocytic leukemia (CLL) (Vlaanderen et al., 2011; Cocco et al., 2010). Relatively low-level exposure to benzene experienced by petroleum distribution workers has also been associated with an increased risk of myelodysplastic syndrome (MDS), some types of which are recognized precursors to AML (Schnatter et al., 2013). Several studies have reported excess morbidity from leukemia or MDS in population groups either residentially or occupationally exposed to petroleum or its products (Schnatter et al., 2012; Barregardt et al., 2009; Talbott et al., 2011; Stenehjem et al., 2014)..While less toxic solvents have been substituted for benzene, it is still a component of petroleum products. Other chemicals implicated in leukemia risk include specific categories of pesticides such as phenoxy-herbicides (Polychronakis et al., 2013; Cocco et al., 2013), as well as chemicals used in the synthetic rubber industry (e.g., formaldehyde) (Polychronakis et al., 2013; Infante PF, 2013).

In terms of lifestyle factors, cigarette smoking has been reported to increase the risk of myeloid leukemia, particularly AML (Musselman et al., 2013; Strom et al., 2012; Fircanis et al., 2014; Slager et al., 2014), while, in one study (Slager et al., 2014), an inverse association was found between current smoking and CLL. In the UK Million Women Study (Kroll et al., 2012), higher levels of smoking were associated with increased risk of MDS but not CLL. The study found no association between alcohol consumption and increased risk of either CLL or MDS. In comparison with non-drinkers, the risk of some lymphoid tumors

(principally non-Hodgkin lymphoma and multiple myeloma) was reduced with increasing amounts of alcohol consumed, a pattern observed in some (Gapstur et al., 2012; Besson et al., 2006) but not all (Heinen et al., 2013 other studies. Thus, there is evidence, not altogether consistent, suggesting that smoking is a risk factor for myeloid forms of leukemia while drinking appears to be associated with reduced risk for lymphoid neoplasms.

We previously reported the results of a case-control study of leukemia risk after radiation exposure among Chornobyl clean-up workers in Ukraine, in which we found increased dose-dependent risks for both CLL and non-CLL leukemias (Romanenko et al., 2008; Zablotska et al., 2013). In the course of the study, we also collected interview data on lifestyle factors and subjects' history of occupational exposure to hazardous chemicals. We report here results of the analysis of these potential non-radiation risk factors in this Ukrainian worker population.

2. Material and Methods

A nested case-control study of leukemia was conducted in a cohort of 110,645 male clean-up workers who resided in one of 5 oblasts of Ukraine (Cherkassy, Chernihiv, Dnipropetrovsk, Kharkiv, Kiev) or Kiev city (Romanenko et al., 2008; Zablotska et al., 2013). The cohort was formed based on data from the Chornobyl State Registry . A total of 162 cases of leukemia was identified among cohort members during the period 1986–2006 and confirmed by an international review panel consisting of 6 hematopathologists from the USA, France, Great Britain, and Ukraine. Incidence density sampling was used to identify and interview 5 controls for each leukemia case from among cohort members without leukemia. Controls were matched to cases by year of birth (+/−2 years) and oblast of residence and had to be alive at the time of diagnosis of the corresponding case.

Individual bone marrow radiation doses for both cases and controls were estimated using a time-and-motion method, known as RADRUE (Realistic Analytical Dose Reconstruction with Uncertainty Estimates) (Kryuchkov et al., 2009; Chumak et al., 2008), based on personal interviews with a special questionnaire to gather data on the workers' exposure history (including place, period, duration of clean-up work and residence in the 70-km zone around the Chornobyl nuclear power plant). Radiation doses were reconstructed for 137 (85%) of 162 confirmed leukemia cases, with little variation in verification rate for different leukemia types (Table 1). Based on the data for cases with reconstructed dose and corresponding controls, a significant linear dose-response was found for all leukemia (ERR/Gy = 1.26 (95% CI: 0.03, 3.58). There were nonsignificant positive dose-response associations for both CLL and non-CLL (ERR/Gy = 0.76 and 1.87, respectively).

Besides the information needed to estimate radiation dose from clean-up work, the questionnaire administered to study subjects included sections designed to collect data on other work-related exposure to radiation either before or after the Chornobyl cleanup work (e.g., in industrial radiography or nuclear energy production). In addition, questions were asked about whether subjects had 'ever worked' in specified Hazardous Industries' (namely, oil refining, chemical plants, resin factories, shoemaking factories, the mechanical repair industry, the electrical industry and Army service). Cohort members were also asked about

'ever' working with three categories of Hazardous Chemicals (organic solvents, pesticides, petroleum products). In addition, questions were asked about lifestyle factors such as history of alcohol consumption and smoking (frequency and intensity).

The study was approved by IRBs in both Ukraine and the U.S., and all subjects gave their signed informed consent.

Statistical methods

To evaluate the possible leukemia risks associated with exposure to factors other than Chornobyl radiation, we carried out categorical analyses of 137 cases and 863 controls with reconstructed radiation doses. Conditional logistic regression adjusted for estimated bone marrow dose (continuous) was used to calculate odds ratios (OR) and 95% confidence intervals (CIs) for all leukemias and leukemia types and subtypes in relation to the following variables: work at hazardous enterprises, contact with hazardous chemicals, marital status, education, alcohol consumption, smoking, type of residency (urban/rural), and exposures to diagnostic x-rays. Statistical significance for main effects and interactions was assessed by likelihood ratio tests, with $P<0.05$ set as the criterion for statistical significance. All tests were two-sided. The models were fitted using the EPICURE statistical package (Preston, 1993).

3. Results

Results of analyses of occupational exposure categories, adjusted for Chornobyl radiation bone marrow dose, are shown in Table 2. Occupational radiation exposure other than Chornobyl was not associated with leukemia risk ($p>0.5$). Similarly, no association was found for work in a "Hazardous Industry" or for exposure to "Hazardous Chemicals" as a group (both $p>0.2$). Results were similar for all leukemia types (not shown). Analyses of pesticides, solvents and 'other chemicals' also showed no association with leukemia risk, although the numbers of exposed subjects were few (<=5) (Table 3) However, we noted that 19 subjects hadreported exposure to petroleum. Detailed analysis (Table 4) showed the odds ratio for petroleum exposure to be significantly elevated for non-CLL leukemias (OR=2.28, 95%CI: 1.13, 6.79, P=0.03). This excess was due to the high OR for myeloid leukemia (OR=3.48; p=.037), especially chronic myeloid leukemia (CML). Petroleum exposure was not associated with risk of CLL ($p>0.5$). We tested for interactions between bone marrow dose and exposure to petroleum but found no indication of a significant modifying effect of radiation ($p=0.58$ from the Likelihood Ratio Test) (data not shown).

Our results from analyses of medical radiation (diagnostic x-rays), and social factors (marital status, education, type of residence (rural/urban)) did not suggest any associations with leukemia (data not shown).

We found no clear relationship with cigarette smoking, for leukemia as a group or by type (Table 5). Although categorical analyses of smoking intensity (packs per day) and pack-years categories did not show significant associations with increased risk of leukemia, the data did suggest a possible decreased risk of non-CLL leukemia with higher smoking intensity; this inverse trend was not statistically significant however ($p=0.08$). Inverse trends

were also seen with alcohol consumption (Supplemental Table 2). As in the case of petroleum, wee found no significant interaction effects between radiation exposure and smoking (p=0.30) or alcohol consumption (p=0.60) (data not shown).

4. Discussion and Conclusions

Previously we reported a statistically significant monotonic increase in radiation risks of leukemia from a case-control study nested in a large cohort of 110,645 male Chornobyl clean-up workers in Ukraine (Romanenko et al., 2008; Zablotska et al., 2013). The current analysis presents the results with regard to independent effects of other potential risk factors, including lifestyle and occupational factors. In this unique cohort from Ukraine, where work conditions may potentially lead to higher levels of hazardous substances, we found that after adjusting for radiation doses from Chornobyl clean-up work, there were no additional exposure-related increases in risk for CLL, either with self-reported employment in a 'Hazardous Industry' or exposure to 'Hazardous Chemicals'. For non-CLL leukemias, however, we found that exposure to petroleum, over and above effects of radiation, was a significant risk factor (OR=2.28, p=0.03), and that this relationship was chiefly due to an increased risk for myeloid leukemia, primarily CML (OR=5.43, p=0.03). Although the relationship is based on relatively few cases (n=30), the association we observed in Ukrainian cleanup workers between petroleum exposure and myeloid leukemia, but not CLL, is generally consistent with findings reported in a number of occupational and environmental groups in other countries (Schnatter et al., 2012; Barregardt et al., 2009; Talbott et al., 2011; Stenehjem et al., 2014). Results from a pooled analysis of benzene exposure in recent petroleum worker cohorts, however, with benzene exposures much below the levels seen previously, did not show associations either CML (Glass et al., 2014) or CLL (Rushton et al., 2014), although one of the pooled studies did find an increased risk of CLL among refinery workers, a group that may have had a more diverse exposure. We should note that, as in several other studies, our data on petroleum exposure come from self-reports. However, a review of the occupations and industries where these subjects were employed showed the reports of exposure to be plausible.

Our findings for smoking and leukemia risk differ from those in some recent studies that found associations with increased risk of AML (Strom et al., 2012; Fircanis et al., 2014; Kroll et al., 2012; Besson et al, 2006). Although after adjustment for radiation we did not observe significant associations with smoking, this may reflect changes in smoking intensity among subjects with the disease or be due to a potential recall bias. The design of the questionnaire was such that it was not possible to determine the timing of reported smoking intensity in relation to the date of diagnosis for cases/reference date for controls. (The same caveat applies to the alcohol data.)The limitations of the retrospective smoking data, especially in view of potential changes in smoking habits related to leukemia diagnosis, do not allow us to rule out the association of smoking and increased risk of AML found in other studies. In addition, we note that our smoking data are not entirely inconsistent with a recent pooled analysis from the InterLymph consortium showing a modest protective effect of current smoking for CLL [36].

Conclusions

Although our study has some limitations due to sample size and lack of details/verification of exposure, our results are among the few epidemiological data on leukemia risk factors in a working Ukrainian population and they add to the accumulating evidence on the leukemogenic effect, especially for non-CLL, of petroleum exposure and its benzene component.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations

AML	Acute Myeloid Leukemia
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myeloid Leukemia
IRB	Institutional Review Board
MDS	Myelodysplastic Syndrome
Non-CLL	non-Chronic Lymphocytic Leukemia
OR	Odds Ratio
RADRUE	Realistic Analytical Dose Reconstruction with Uncertainty Estimates
USA	United States of America

Highlights

- A unique population - a cohort of 110,645 Chernobyl clean-up workers from Ukraine
- Followed 1986–2006 for leukemia, interviewed about non-radiation risk factors
- Petroleum exposure increased risk for non-CLL leukemias, particularly CML
- No risk factor other than radiation was found for CLL

Table 1

Distribution of Cases of Leukemia Among Ukrainian Chornobyl Cleanup Workers by Subtype, 1986–2006.

Cell Type	Confirmed[a] cases	Cases with doses[b] (% confirmed cases)
All leukemias	**162**	137 (84.6)
Non-CLL[c]	73	58 (79.5)
Including:		
Myeloid leukemia	48	40 (83,3)
Acute myeloid leukemia (AML)[d]	20	16 (80.0)
Chronic myeloid leukemia	28	24 (85.7)
Acute lymphocytic leukemia	8	6 (75.0)
Acute leukemia otherwise not specified	11	7 (63.6)
Other chronic leukemia[e]	6	5 (83.3)
CLL	89	79 (88.8)

[a] Cases confirmed by the International Hematopathology Panel.

[b] Bone marrow doses estimated by RADRUE method from dosimetric questionnaires of participants or their proxies.

[c] CLL – Chronic lymphocytic leukemia

[d] Combined AML group includes 4 Myelodysplastic syndrom (MDS) RAEB-t cases.

[e] 1 Hairy cell leukemia initially was in CLL group and then was transferred to Other chronic leukemia group.

Table 2

Odds Ratios and 95 % Confidence Intervals for Exposure to Hazardous Factors and leukemia (n=137)

Subtype of Leukemia	Variable	Cases	%	Controls	%	OR[a]	95 % CI
All leukemias	Radiation exposure[b]. No	113	87.6	749	87.1	1	
	Yes	16	12.4	111	12.9	0.82	0.46 – 1.49
	Hazardous industry[c] No	111	86.7	718	83.4	1	
	Yes	17	13.3	143	16.6	0.71	0.41 – 1.26
	Hazardous chemicals[d] No	102	78.5	666	77.5	1	
	Yes	28	21.5	193	22.5	1.03	0.64 – 1.65
Non CLL	Radiation exposure No	47	88.6	329	87.2	1	
	Yes	6	11/3	48	12.7	0.80	0.31 – 2.06
	Hazardous industry No	46	88.4	311	82.5	1	
	Yes	6	11.5	66	17.5	0.56	0.22 – 1.40
	Hazardous chemicals No	39	72.2	293	77.5	1	
	Yes	15	27.7	85	12.5	1.48	0. 75 – 2.92
CLL	Radiation exposure No	66	86.8	420	86.9	1	
	Yes	10	13.1	63	13.0	1	0.48 – 2/14
	Hazardous industry No	65	85.5	407	84.1	1	
	Yes	11	14.5	77	15.9	0.84	0/41 – 1.74
	Hazardous chemicals No	63	82.9	373	77.5	1	
	Yes	13	17.1	108	22.5	0.74	0.38 – 1.45

[a] OR from conditional logistic regression with adjustment for radiation dose to the bone marrow lagged by 2 years.

[b] data on radiation exposure (other than Chornobyl) are missing for 8 cases and 3 controls

[c] data on hazardous industry (oil refining, chemical plants, resin factories, shoemaking factories, the mechanical repair industry, the electrical industry and Army service) exposure are missing for 9 cases and 2 controls

[d] data on hazardous chemicals exposure are missing for 7 cases and 4 controls

Table 3

Odds Ratios and 95 % Confidence Intervals for Exposure to Hazardous Chemicals and leukemia (n=137)

Variable (chemical)	Cases	%	Controls	%	OR[a]	95 % CI
Pesticides[b]						
No	129	96.2	821	95.2	1	
Yes	5	3.8	41	4.8	0.78	0.28 – 2.13
Solvents[b]						
No	133	99.2	846	98.1	1	
Yes	1	0.8	16	1.85	0.30	0.03 – 3.14
Petrol[b]						
No	115	85.8	765	88.7	1	
Yes	19	14.2	97	11.3	1.56	0.86 – 2.81
Other chemicals[b]						
Yes	129	96.3	807	93.6	1	
No	5	3.7	55	6.4	0.52	0.20 – 1.40

[a] OR from conditional logistic regression with adjustment for radiation dose to the bone marrow lagged by 2 years.

[b] data on hazardous chemicals exposure are missing for 3 cases and 1 control

Table 4

Odds Ratios and 95 % Confidence Intervals for Petrol Exposure by subtypes of leukemia (n=137).

Subtype of leukemia	Cases	%	Controls	%	OR[a]	95 % CI
All leukemias[b]						
No	115	85.8	765	88.7	1	
Yes	19	14.2	97	11.3	1.56	0.86 – 2.81
Non-CLL[c]						
No	45	81.8	339	89.4	1	
Yes	10	18.2	40	10.6	2.28	1.13 – 6.79
Including:						
Myeloid leukemia						
No	30	81.1	229	90.9	1	
Yes	7	18.9	23	9.1	3.48	1.09 – 11.12
Acute myeloid leukemia						
No	11	84.6	85	88,5	1	
Yes	2	15.4	11	11.5	1.85	0.29 – 11.72
Chronic myeloid leukemia						
No	19	79.2	144	92.3	1	
Yes	5	20.8	12	7.7	5.43	1.11 – 26.54
CLL						
No	70	88.6	426	88.2	1	
Yes	9	11.4	57	11.8	1.03	0.45 – 2.33

[a] OR from conditional logistic regression with adjustment for radiation dose to the bone marrow lagged by 2 years.

[b] data on petroleum exposure are missing for 3 cases and 1 control

[c] Includes all types of myeloid leukemia, non lymphoid chronic leukemia, leukemia otherwise not specified,

Table 5

Odds ratios and 95 % Confidence intervals for smoking categories and leukemia subtypes

Variable	All leukemias			CLL			non-CLL		
	Cases N (%)	Controls N(%)	OR[a] (95% CI)	Cases N (%)	Controls N(%)	OR [a] (95% CI)	Cases N (%)	Controls N(%)	OR [a] (95% CI)
Smoking status[b]									
Never smoked[c]	35	217	reference	19	124	reference	16	93	reference
Ever smoked	95	646	1.09 (0.72 – 1.67)	57	360	1.09 (0.62 – 1.92)	38	286	0.72 (0.38 – 1.37)
Former smoker	65	311	1.25 (0.77 – 2.02)	35	191	1.08 (0.56 – 2.10)	30	120	1.46 (0.72 – 2.93)
Current smoker	30	335	0.66 (0.37 – 1.18)	19	124	1.20 (0.57 – 2.53)	8	166	0.25 (0.09 – 0.69)
Regular smoking (ever smoked vs never smoked)									
<1 pack/day	53	281	1.11 (0.68 – 1.82)	31	157	1.27 (0.65 – 2.45)	22	124	0.94 (0.45 – 1.97)
>1 pack/day	36	340	0.67 (0.39 – 1.14)	21	188	0.88 (0.43 – 1.80)	15	152	0.46 (0.20 – 1.05)
Pack-years for ever smoked[d]									
0	35	217	Reference	19	124	Reference	16	93	Reference
>0–15	30	190	1.39 (0.82 – 2.36)	10	103	1.17 (0.60 – 2.30)	20	87	0.81 (0.38 – 1.70
>15–30	32	207	1.38 (0.79 – 2.39)	23	112	0.79 (0.35 – 1.78)	9	95	0.43 (0.18 – 1.02)
>30	25	221	0.98 (0.55 – 1.74) P, trend>0.5	17	128	1.04 (0.52 – 2.07) P, trend=0.281[b]	8	93	0.39 (0.15 – 0.98) P, trend=0.080[b]

[a] OR from conditional logistic regression with adjustment for radiation dose to the bone marrow lagged by 2 years.

[b] data on smoking are missing for 7 cases

[c] reference group is “never smoked” for all models

[d] data on pack-years are missing for 8 cases and 28 controls0

5.4 Оцінка ризиків раку щитоподібної залози у учасників ліквідації наслідків аварії на ЧАЕС в Україні (1988-2012 рр)

Conclusion: Our 3-steps approach identified one exposure associated with lower FEV1, postnatal blood copper level, while an agnostic ExWAS reported no significant association. Further research is needed to quantify the efficiency of this approach.

Risk of thyroid cancer among Chernobyl clean-up workers in Ukraine

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OPS 26: Radiation, EMF, cancer and mortality, Room 114, Floor 1, August 26, 2019, 4:30 PM - 5:45 PM

Although much is known about the radiation-related risk of thyroid cancer in those exposed at young ages, less is known about the risk due to adult exposure. Among Japanese atomic bomb survivors and in some other higher dose groups there is little or no statistical evidence of a radiation dose-response for thyroid cancer among those exposed in adulthood. In contrast, a strong and significant dose-response was found in a case-control study of Belarusian, Russian and Baltic clean-up workers exposed as a result of the 1986 Chernobyl nuclear power plant accident. To improve the characterization of thyroid cancer risk following adult exposure, we conducted a nested case-control study (149 cases; 458 controls) in Ukrainian clean-up workers. Individual thyroid doses due to external irradiation, inhalation during the cleanup mission, and intake of I-131 during residence in contaminated settlements were calculated for all study subjects (total dose mean 199 mGy; range 0.15 mg to 9 Gy). Our preliminary findings suggest a non-significantly increased total radiation dose-response for thyroid cancer (excess relative risk [ERR] =0.40; 95% confidence interval: -0.05, 1.48; p=0.12). Time since exposure significantly modified this association so that less time since exposure was associated with a higher ERR/Gy. Further analyses are being conducted to characterize the dose-response relationships according to source of exposure and histological subtype.

Long-term exposure to road traffic noise, air pollution and adiposity markers: a joint analysis of HUNT3, Lifelines and UK Biobank

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TPS 781: Health effects of noise, Exhibition Hall, Ground floor, August 27, 2019, 3:00 PM - 4:30 PM

Background/Aim

The role of road traffic noise on adiposity remains understudied. We aimed to investigate long-term exposure to road traffic noise, air pollution and adiposity in three European cohorts.

Methods

HUNT3, Lifelines and UK Biobank were established in 2006-2013. For all three cohorts, residential road traffic noise (Lden) for 2009 was modelled from a standardised European noise assessment framework. Exposures to PM10 for 2007 and PM2.5 for 2010, were estimated from land use regression models. Adiposity markers including body mass index and waist circumference were measured at baseline. Obesity and central obesity status was subsequently derived. Regression models were fitted in each cohort, adjusting for the same set of demographic and lifestyle covariates including education, with further adjustments for air pollution in the main model.

Results

The main analyses included 25,629 participants of HUNT3, 61,032 of Lifelines and 404,863 of UK Biobank, with a mean age of 43-56 years and mean Lden of 49-56 dB(A) across cohorts. 15% of Lifelines participants were obese, comparing to 24% in the other two. 34% of UK Biobank and Lifelines participants had central obesity and 47% in HUNT3. In UK Biobank, per 10 dB(A) higher of Lden: BMI was higher by 0.144(95%CI: 0.110-0.178), waist circumference higher by 0.271(95%CI: 0.187-0.355), odds of obesity was 1.059(95%CI: 1.041-1.077) and of central obesity was 1.051(1.035-1.068).These associations were independent of air pollution, and stronger among females and those with low physical activity. No associations were found in the other two cohorts, except for central obesity in males (1.094, 95%CI: 1.000-1.207) in HUNT3. In both UK Biobank and Lifelines, significant positive associations were observed between PM and central obesity, independent of noise exposure.

Conclusions

Higher exposure to road traffic noise and/or air pollution was independently associated with higher adiposity. Longitudinal analyses are currently being conducted to help with causal inference.

Neonicotinoid exposure in the U.S. general population

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[1]*CDC*

TPS 623: Exposures to pesticides, Johan Friso Foyer, Floor 1, August 26, 2019, 3:00 PM - 4:30 PM

Background: Neonicotinoids, agricultural insecticides, are also used for flea control in household pets. Neonicotinoids have become popular replacements for other insecticides (e.g., organophosphates, carbamates), and use may be on the rise.

Methods: We measured urinary concentrations of six neonicotinoid biomarkers: acetamiprid, clothianidin, imidacloprid, thiacloprid, N-desmethyl-acetamiprid, and 5-hydroxy-imidacloprid in 3,038 samples from participants 3 years and older from the 2015–2016 National Health and Nutrition Examination Survey. We calculated distribution percentiles and used regression models to evaluate associations of various demographic parameters with urinary concentrations above the 95th percentile (a value that represents higher than average concentrations) of neonicotinoid biomarkers.

Results: The weighted detection frequencies were 35% (N-desmethyl-acetamiprid), 19.7% (5-hydroxy imidacloprid), 7.7% (clothianidin), 4.3% (imidacloprid), and <0.5% (acetamiprid and thiacloprid). Concentrations ranged from <0.40–40.4 µg/L (5-hydroxy imidacloprid), <0.20–34.7 µg/L (N-desmethyl-acetamiprid), <0.20–31.1 µg/L (clothianidin), and <0.4–4.94 µg/L (imidacloprid). Children 3–5 year old who fasted <8 hours were more likely to have N-desmethyl-acetamiprid concentrations above the 95th percentile than adolescents (adjusted odds ratio (OR) = 3.12; 95% confidence interval [CI], (0.98-9.98) and adults (OR = 4.29; 95% CI, (2.04-9.0)). Asians were two times more likely than non-Asians to have concentrations above the 95th percentile of N-desmethyl-acetamiprid and 5-hydroxy-imidacloprid (OR = 1.94; 95% CI, (1.08-3.49) and 2.25; 95% CI, (1.44-3.51)), respectively. The probabilities of having N-desmethyl-acetamiprid and 5-hydroxy-imidacloprid concentrations above the 95th percentile in the summer were 1.55 and 2.43 times higher than in winter, respectively.

Conclusions: These first reference ranges of neonicotinoid biomarkers in the U.S. general population 3 years of age and older suggest human exposure to select neonicotinoids. The data also suggest metabolites are better biomarkers of background exposure than the parent compounds themselves. Compared to others, young children and Asians

6. ДОСЛІДЖЕННЯ ГЕНЕТИЧНИХ ЕФЕКТІВ ОПРОМІНЕННЯ СЕРЕД НАЩАДКІВ ОСІБ, ЩО ЗАЗНАЛИ ОПРОМІНЕННЯ ВНАСЛІДОК АВАРІЇ НА ЧАЕС

Метою спільного американо-українського дослідження генетичних ефектів опромінення серед учасників ліквідації наслідків аварії на ЧАЕС в Україні та їхніх нащадків (ТРІО) було дослідити геномні ушкодження в клітинах крові та епітелію ротової порожнини у кожного члена сім'ї у звязку із дозою опромінення, отриманої батьками до моменту концепції, а також за 3 місяці до концепції. Дизайн та методи дослідження представлені у **підрозділі 6.1**. Доза була оцінена з використанням відповідних методів дозиметрії, основаних на аналізі даних персонального анкетування (RADRUE, математичне моделювання). Тільки сім'ї із дітьми, народженими через 42 тижні і більше після опромінення батьків були включені у дослідження. Дітям мало бути не менше 18 років на момент опитування.

Метою дослідження було оцінити маркери генетичних ушкоджень, які могли передатись нащадкам опромінених батьків, насамперед де-ново мутацій, визначених шляхом секвенування цілого геному у опромінених батьків і їхніх нащадків і оцінки надлишку частоти в залежності від дози на гонади батьків. Послідовно формувалися групи: 1) опромінений батько і неопромінена мати (група А); 2) опромінена мати і неопромінений батько (група В); 3)обидва батьки опромінені (група С); 4) обидва батьки неопромінені (група D); 5) один з батьків із з високою дозою опромінення, в т.ч. із гострою променевою хворобою в анамнезі. Три компоненти дози опромінення (зовнішнє за рахунок виконання робіт, зовнішнє за період перебування в Прип'яті, внутрішнє) були реконструйовані з використанням методів, які засвідчили свою відповідність в попередніх аналітичних епідеміологічних дослідженнях (RADRUE, його модифікація ROCKVILLE, математичні моделі для оцінки внутрішнього опромінення).

Результати аналізу даних дослідження трансгенераційних ефектів опромінення та висновок на їхній основі представлено у **підрозділі 6.2.**

За даними проведеного дослідження було встановлено, що єдиним суттєвим фактором, який суттєво впливає на рівень визначених де ново мутацій, був вік батька на час проведення дослідження. Хоча в проведеному аналізі не було визначено залежності частоти де ново мутацій у нащадків учасників ліквідації наслідків аварії від дози опромінення, отриманої батьками, подальші дослідження із включенням більшої кількості суб’єктів можуть дійти уточнених висновків.

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6.1 Дослідження можливого впливу батьківського опромінення на зародкову лінію дітей, народжених від ліквідаторів та евакуйованих внаслідок Чорнобильської катастрофи (дизайн та методи дослідження)

Study Design

Field Study of the Possible Effect of Parental Irradiation on the Germline of Children Born to Cleanup Workers and Evacuees of the Chornobyl Nuclear Accident

Dimitry Bazyka, Maureen Hatch, Natalia Gudzenko, Elizabeth K. Cahoon, Vladimir Drozdovitch, Mark P. Little, Vadim Chumak, Elena Bakhanova, David Belyi, Victor Kryuchkov, Ivan Golovanov, Kiyohiko Mabuchi, Iryna Illienko, Yuri Belayev, Clara Bodelon, Mitchell J. Machiela, Amy Hutchinson, Meredith Yeager, Amy Berrington de Gonzalez, and Stephen J. Chanock*

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Although transgenerational effects of exposure to ionizing radiation have long been a concern, human research to date has been confined to studies of disease phenotypes in groups exposed to high doses and high dose rates, such as the Japanese atomic bomb survivors. Transgenerational effects of parental irradiation can be addressed using powerful new genomic technologies. In collaboration with the Ukrainian National Research Center for Radiation Medicine, the US National Cancer Institute, in 2014–2018, initiated a genomic alterations study among children born in selected regions of Ukraine to cleanup workers and/or evacuees exposed to low–dose-rate radiation after the 1986 Chornobyl (Chernobyl) nuclear accident. To investigate whether parental radiation exposure is associated with germline mutations and genomic alterations in the offspring, we are collecting biospecimens from father-mother-offspring constellations to study de novo mutations, minisatellite mutations, copy-number changes, structural variants, genomic insertions and deletions, methylation profiles, and telomere length. Genomic alterations are being examined in relation to parental gonadal dose, reconstructed using questionnaire and measurement data. Subjects are being recruited in exposure categories that will allow examination of parental origin, duration, and timing of exposure in relation to conception. Here we describe the study methodology and recruitment results and provide descriptive information on the first 150 families (mother-father-child(ren)) enrolled.

Chornobyl (Chernobyl); genetic risk; germline mutations; low–dose-rate radiation; parent-offspring constellations; preconception exposure; Ukraine

Abbreviations: DOB, date of birth; NCI, National Cancer Institute; NRCRM, National Research Center for Radiation Medicine.

Identifying the full extent of ionizing radiation–related health effects is critical for handling of nuclear accidents, radiation protection standards, and clinical practice. Pioneering experimental studies of transgenerational effects were carried out in 1927 (1) and 1958 (2), but until recently human research on transgenerational radiation effects following parental exposure has been limited. Sievert, in a 1958 paper prepared for the International Commission on Radiological Protection (3), pointed to the scarcity of data on possible genetic effects of radiation in humans. Sixty years later, this remains an important and controversial issue, particularly in the wake of the Chornobyl (Chernobyl) and Fukushima nuclear power plant accidents, which occurred in 1986 and 2011, respectively. Intervening studies have been confined to studies of disease phenotypes and minisatellite mutation rates in Japanese atomic bomb survivors, Chornobyl-exposed groups, and offspring of childhood cancer survivors, mostly exposed to high doses/rates (4). With the

advent of next-generation sequencing technologies, which can survey nearly the entire human genome, it is possible to more thoroughly explore mutations to the germline resulting from protracted moderate- and low-dose exposure—a question of long-standing concern to radiation scientists and public health officials.

Historical data in mice have established evidence of a transgenerational effect, but only under experimental conditions—most of which do not approximate the type and duration of radiation exposure incurred by the Chornobyl cleanup workers (5). Early studies following the Chornobyl accident provided preliminary data that warrant follow-up (6–10). In one underpowered study, Jeffreys et al. (6) examined germline mutations, focusing on mutations in minisatellites, proposed as biomarkers of genomic instability. In small studies, excess numbers of minisatellite events have been reported among children born after radiation exposure to parents in Chornobyl-exposed areas in Ukraine and Belarus (7–9), as well as among offspring of other radiation-exposed groups (9, 10). Minisatellite data from murine work suggested a lower doubling dose (the radiation dose required to double the spontaneous mutation rate) than expected (2, 11–13). Concerns were raised regarding the adequacy of the dosimetry in the positive minisatellite studies—especially when both parents were exposed—as well as potential confounding by sex, paternal age at conception, age of offspring, and putative chemical pollutants (4). Positive results contrast with negative findings in the offspring of Chornobyl cleanup workers (14, 15), although the cleanup worker studies had limited statistical power with lower exposures.

Human research on transgenerational effects, namely effects on offspring born to 1 or both radiation-exposed parents, has been primarily focused on disease outcomes, including endpoints such as congenital malformations, cancer, and premature mortality. Studies using conventional approaches have included offspring of Japanese atomic-bomb survivors, childhood cancer survivors exposed to radiotherapy, and radiation workers (4). Most studies of transgenerational effects have been null or showed elevated risks that were not statistically significant (4, 16).

Offspring of Japanese atomic-bomb survivors (the F_1 cohort) have also been studied for increases in mutations, yielding null or statistically insignificant findings (17–20). There have been few studies that have addressed possible transgenerational effects of parental irradiation using next-generational sequencing technologies, and these have been small in size and scope. The most recent F_1 study (21), which used next-generational sequencing to detect de novo single nucleotide variants, found no increase in de novo single nucleotide variants in the children but was based on only 3 father-mother-offspring constellations. Using high-density single nucleotide polymorphism array technology in a population exposed to low doses of cesium-137 from the Goiânia radiological accident in Brazil, Costa et al. (22) reported an increase in de novo copy-number variants in the offspring of exposed relatives.

While no firm conclusions on heritable disease or mutation frequencies can yet be drawn, the extent of possible effects of radiation on the offspring of exposed parents and the subsequent generations is a continuing concern. The Division of Cancer Epidemiology and Genetics of the US National Cancer Institute (NCI), in collaboration with the National Research Center for Radiation Medicine (NRCRM) in Kyiv, Ukraine, initiated a family study to investigate the transgenerational effects of radiation exposure in the offspring of cleanup workers and evacuees who were exposed before conception to external and internal radiation from the Chornobyl nuclear accident; this derives from successful joint efforts, such as studies of leukemia among cleanup workers (23–25).

OBJECTIVE

The purpose of the NCI-NRCRM Study is to investigate, among 450 father-mother-offspring family constellations (predominately trios), the relationship between parental gonadal radiation dose and genomic alterations among children born after the Chornobyl accident and to determine whether parental exposure is associated with germline mutations and de novo alterations in offspring. Family constellations recruited between 2014 and 2018 will be evaluated in a series of genetic analyses designed to characterize the scope and types of events and to determine whether they are related to paternal or maternal exposure. Study outcomes include de novo mutation rates, minisatellite mutations, copy-number alterations, structural variants, telomere length, and clonal hematopoiesis. Methylation changes associated with genomic imprinting will also be examined.

Study design

The study was designed to measure genomic alterations in blood and buccal samples from each member of the family constellation (consenting father, mother, and child(ren)) and to correlate them with estimates of parental gonadal dose from the time of the Chornobyl accident to the time of conception, as well as the 3-month period prior to conception, reconstructed using existing records and interview data.

Study population

Study parents are selected from representative populations in the NRCRM's Clinico-Epidemiologic Registry. The Clinico-Epidemiologic Registry, established in 1992, performs long-term extended follow-up of persons exposed to ionizing radiation from the nuclear power plant accident at Chornobyl, drawn from those listed in the Chornobyl State Registry (26) and resident principally in Kyiv City or its oblast (surrounding region). Only families with offspring born 42 weeks after the last significant Chornobyl-related parental exposure are eligible to participate. Offspring must be older than 18 years of age at the time of interview. Families with parents or offspring found to have cancer will be excluded from the analysis because of the potential for treatment with radiation and chemotherapy, both of which can adversely affect the active bone marrow and therefore derived estimates of mutational load.

Subjects are categorized into 5 groups based on preliminary estimates of exposure from the Chornobyl State

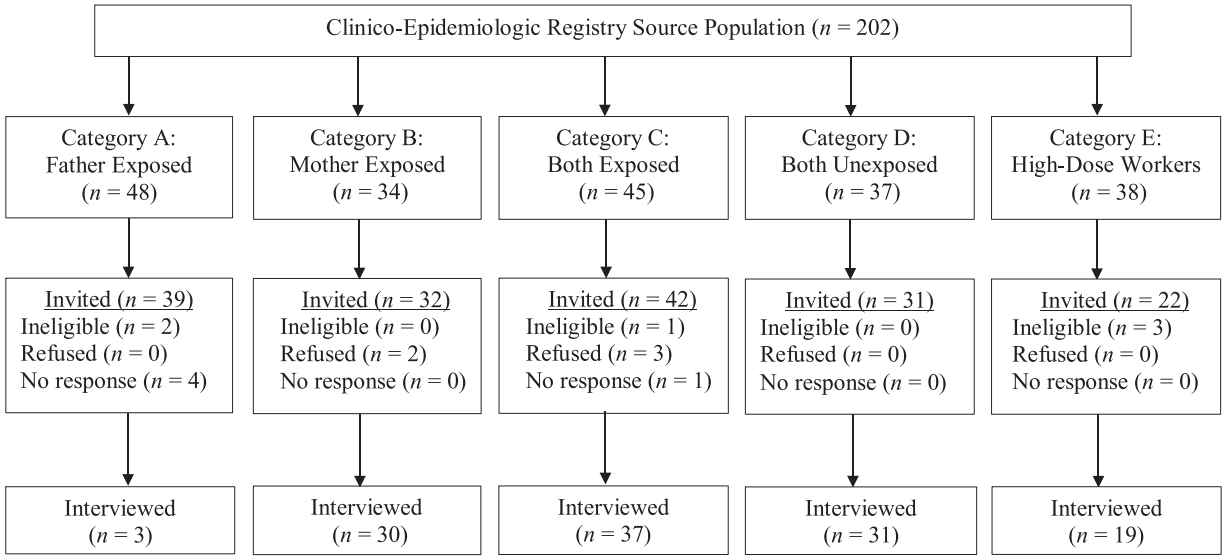

Figure 1. Enrollment of families into a study of transgenerational effects of parental irradiation during the Chornobyl nuclear accident, Ukraine, 2014–2018.

Registry and other sources: 1) exposed father, unexposed mother (category A); 2) exposed mother, unexposed father (category B); 3) both parents exposed (category C); 4) both parents unexposed (category D); and 5) high-dose emergency workers, including those with acute radiation syndrome (category E). Families in group D were matched to those in groups A–C by age and residence but had no known history of radiation exposure from the accident and were drawn from the Clinico-Epidemiologic Registry.

Figure 1 outlines the enrollment process for the first 150 families recruited. As the data show, the response rate among those invited to participate to date has been 85% or better in all exposure categories.

Data collection

Each prospective parent participant has been asked to complete a questionnaire for collection of demographic data and data on non–radiation-related risk factors that could also possibly result in germline mutations, including history of cancer, smoking history, alcohol consumption, employment in "hazardous industries" (e.g., oil refining, chemical factories, rubber factories), and employment involving "hazardous exposures" (defined as exposure to gasoline (petrol), organic solvents, and agricultural pesticides). The parents completed separate dosimetry questionnaires administered by a qualified interviewer, such as a former cleanup worker or employee of the Chornobyl nuclear power plant. All questionnaire data are double-entered, cross-checked, and, if necessary, reconciled with the original paper forms.

For estimation of radiation exposure, subjects have been asked to provide detailed information on their work history during the cleanup mission in the 30-km zone around the Chornobyl power plant, their outdoor/indoor activities (hour by hour) while in Pripyat (the town closest to the plant and the residence of most plant employees and their families), and residential and dietary history in contaminated areas other than Pripyat up to the time of the child's birth. Because work history and behavior data are being sought many years after the accident, steps are being taken to increase the accuracy of information obtained during the personal interviews. To help interviewees recall their activities while in the Chornobyl zone, supporting material has been used, including booklets with maps, schemes, and photographs of the facilities and buildings within the 30-km zone at various periods of the cleanup, a dictionary of jargon and terms used by cleanup workers, and photographs of dosimeters. The interviewers have also used special questions to stimulate respondents' recall (e.g., "What did you see around you?"; "How far were you from [a particular location]?"). Questionnaire data have been subsequently reviewed and interpreted by knowledgeable expert dosimetrists. Dose reconstruction has also incorporated information on radiation fields in the environment: exposure rates in air measured at different locations and times within the 30-km zone (27) and deposition densities of cesium-137 in places of residence (28), as well as deposition densities of other γ-emitted radionuclides (29).

Quality control

An operations manual was prepared for tracing, contacting, and inviting subjects to participate, as well as interviewing (both epidemiologic and dosimetry questions). The manual covers quality control of specimen collection, labeling, and handling for ongoing training and supervised review.

The interview staff underwent primary training with periodical retraining and were instructed in proper procedures

for tracing study subjects, contacting prospective subjects, interviewing (filling in the questionnaires), entering data into the database, and careful specimen labeling. Study personnel were instructed to monitor the correct identity of all study subjects at all stages of registration, interviewing, sample collection, entry of data into the database, dose reconstruction, and transfer of samples to the NCI after anonymization. A unique individual number was assigned to each subject in the study and was used for barcoding of blood and buccal samples. There was only 1 instance of double labeling, which involved labeling of the sample of a participant's spouse with the same barcode. Following this event, additional quality control procedures were implemented to avoid recurrence of this error.

An important control point was the verification of the recorded dates of birth for the offspring by cross-matching the questionnaire data of each parent and child. Such reconciliation was carried out at the stage of registration of completed questionnaires along with data encoding at the Data Coordinating Center. Quality control procedures at the stage of data entry into the database consisted of 3 sequential stages—coding of questionnaires, entry of data into the database, and quality control of the data entered. The coding procedure included checking the completeness of data filling, checking logical errors in the records, bringing records and data formats into accordance with the dictionary, and encoding data according to the dictionary.

Dose reconstruction

Doses of radiation to the parental gonads are reconstructed from the time of the accident on April 26, 1986, to 2 time points: 51 weeks before the child's date of birth (DOB-51) and 38 weeks before the child's date of birth (DOB-38). The DOB-38 time point identified the period prior to conception of the offspring, while DOB-51 marked the point 3 months before conception. The difference between these 2 measures was intended to develop a dose estimate for the 3-month period before conception, when there could be potential exposure to paternal spermatids, whereas the DOB-51 dose corresponds to the dose to spermatogonial stem cells. For maternal exposure, the only relevant time point is DOB-38.

Doses are estimated for 3 components of exposure: 1) external irradiation during the cleanup mission; 2) external irradiation during residence in Pripyat (where exposure levels are likely to be particularly high), before and during evacuation, if applicable; and 3) external irradiation and ingestion of cesium isotopes due to residence in a contaminated area other than Pripyat. Calculation of gonadal dose to parental subjects has used analytical dose reconstruction methods developed for and successfully implemented in previous NCI-NRCRM collaborative projects—methods such as realistic analytical dose reconstruction with uncertainty estimation (RADRUE) (27) and its further development, Rockville, based on location-specific exposure rates and irradiation times. Doses due to residence in contaminated areas were estimated on the basis of residential history and consumption of local foods (e.g., milk, dairy products, meat, and vegetables) used in the study of thyroid cancer among Ukrainian cleanup workers. Organ doses to the gonads were estimated for both external and internal exposure, with external exposure being strongest.

Dosimetry has been completed for the 150 enrolled families. Table 1 shows characteristics associated with the DOB-38 gonadal doses from all exposure pathways combined that were reconstructed for fathers and mothers from each of the 5 categories.

Genomic analyses

All interviewed subjects provided both blood and buccal samples; the former were collected by a certified phlebotomist in PAXgene (BD Biosciences, Radnor, Pennsylvania) and K2-ethylenediaminetetraacetic acid tubes and transferred to the laboratory at the NRCRM for storage at −80°C. In addition, the interviewer collected samples of saliva using the Oragene OG-500 kit (DNA Genotek, Ottawa, Ontario, Canada). Blood and buccal samples were shipped in batches to the NCI Cancer Genomics Research Laboratory (Gaithersburg, Maryland) for DNA extraction from 2 mL of whole blood in ethylenediaminetetraacetic acid via the Qiagen QIAsymphony SP automated instrument (Qiagen NV, Venlo, the Netherlands). DNA was extracted from saliva in Oragene collection tubes (DNA Genotek) by means of the Qiagen QIAsymphony SP automated instrument using a standard kit and custom protocol.

DNA derived from blood or buccal samples will be sequenced to an average coverage depth of 80× across the genome—known as whole genome sequencing. Single nucleotide variants will be called using a standardized pipeline based on GATK HaplotypeCaller and a filtering strategy modified from recent reports (30, 31). Genomic analyses of the family sets (i.e., parents and offspring) are conducted by the NCI Cancer Genomics Research Laboratory using collected blood and buccal samples and will be tested for associations with measurements and interview-based estimates of parental preconceptional gonadal dose.

Endpoints

Our aim is to identify markers of transgenerational genetic effects in offspring of parents exposed before conception to radiation from Chornobyl, by examining the following endpoints:

1. *De novo mutations* (point mutations, small insertions/deletions, and mutations in mini- and microsatellites) will be assessed by whole genome sequencing in the families (father-mother-offspring(s)) of exposed parents and offspring to test for an increased frequency in relation to paternal/maternal gonadal dose.

2. *Large (>1.5 megabases) copy-number changes* will be assessed using the Illumina Global SNP Array, version 1 (Illumina, Inc., San Diego, California), based on a modification of the methods described by Jacobs et al. (32) and Machiela et al. (33). The method detects both germline and somatic (mosaic) events.

Table 1. Parental Gonadal Doses of Radiation Incurred During the Chornobyl Nuclear Accident, Reconstructed From the Time of the Accident to 38 Weeks Before the Child's Birth (All Exposure Pathways), by Exposure Category, Ukraine, 2014–2018

Exposure Category	No. of Families	No. of Children	Radiation Dose, mGy			
			Fathers		Mothers	
			AM	Median (Range)	AM	Median (Range)
A (exposed father, unexposed mother)[a]	33	38	140.0	37.0 (0.4–730.0)	0.9	0.8 (0–6.6)
B (exposed mother, unexposed father)[a]	30	41	1.1	0.8 (0–6.4)	16.0	12.0 (2.2–64.0)
C (both parents exposed)	37	47	320.0	80.0 (0.9–2,760.0)	22.0	14.0 (0.7–260.0)
D (both parents unexposed)[a]	31	37	0.6	0.6 (0–1.5)	0.8	0.6 (0.2–3.0)
E (high-dose emergency workers)	19	22	870.0	480.0 (17.0–4,140.0)	55.0	0.9 (0.3–550.0)
Total	150	185	210.0	6.4 (0–4,140.0)	16.0	2.4 (0–550.0)

Abbreviation: AM, arithmetic mean.
[a] Includes children with a parental gonadal dose of 0.

3. *Telomere length* will be examined to test for alterations in telomere length in parents and offspring, assayed using quantitative polymerase chain reaction (34, 35).

4. *Clonal hematopoiesis* is an age-related phenomenon wherein recurrent somatic point mutations occur in a subpopulation of blood cells in specific genes. It can increase risk of cardiovascular disease (36) and hematological malignancies (37). We will investigate whether radiation exposure increases the occurrence of clonal hematopoiesis.

5. *Methylation status* in parents and offspring will be evaluated with the Illumina Infinium MethylationEPIC BeadChip array (Illumina, Inc.), which interrogates over 850,000 CpG sites in the genome. We will test for differential imprinting associated with parental radiation exposure. The analyses will explore the relationships of methylation level at a single CpG site with parental radiation dose, age of the parents at conception, and global measures of methylation.

RETURN OF RESULTS AND DATA-SHARING

Potentially participating families are told in advance, and the informed consent form explicitly states, that there will be no return of results of the genetic testing. This approach was adopted because at present the genomic studies planned have no known clinical significance. Only in the event that something of medical importance is found, as determined by guidance from the American College of Medical Genetics, will the subjects and their physicians at NRCRM be informed. Any incidental finding of medical importance will be referred to the institutional review board in Ukraine, which will decide what, if any, further steps are to be taken.

In accordance with National Institutes of Health policy, delinked anonymized results of genetic testing of families will be submitted through the registered access system of the Database of Genotypes and Phenotypes (National Center for Biotechnology Information, Bethesda, Maryland), by which approved investigators can access data according to an agreed-upon data user's certificate. This stipulates strict adherence to standard confidentiality procedures by bona fide researchers.

Statistical analysis

We will investigate the relationship between parental preconceptional radiation dose—both overall and by parental origin—and the extent of genetic alterations in the offspring using regression models. Models will examine differences in the genomic mutations and alterations (e.g., total de novo mutations derived from whole-genome sequencing data, mutations restricted to minisatellite frequencies) in the offspring, with adjustment for relevant variables such as paternal and maternal age at conception, time between exposure and conception, sex, alcohol or tobacco use, and age of the offspring. The analytical approach will jointly model paternal and maternal measures of radiation dose as separate covariates in the same model to ensure that de novo mutation effect estimates account for the radiation dosage of both parents.

Estimates of statistical power are given in the Web Appendix (available at https://academic.oup.com/aje). Web Table 1 presents paternal, maternal, and conjoint dose distributions, based on the first 150 families (185 children) enrolled in the study. For paternal and maternal doses, the power of a 2-sided trend test for all de novo mutations with $\alpha = 0.05$ in many cases approaches 100%, even with only the 150 families (185 children) already assembled (Web Table 2). Since paternal age will play a significant role, based on analysis of trios from Iceland by Kong et al. (38) and Jonsson et al. (39), as well as the Inova patient trios (40), maternal age is less likely to influence the development of de novo mutations (38, 39). For minisatellite mutations, assuming a doubling dose of 1 Gy, for paternal exposure the power of a 1-sided trend test with $\alpha = 0.05$ is over 90% for the sample of 450 families (555 children), and 77% and 47% for the smaller samples of 250 families

Table 2. Cross-Tabulation of Parental Gonadal Doses of Radiation Incurred During the Chornobyl Nuclear Accident, Reconstructed From the Time of the Accident to 38 Weeks Before the Child's Birth[a], Ukraine, 2014–2018

Father's Dose, mGy	Mother's Dose, mGy						
	0.00–0.99	1.00–4.99	5.00–9.99	10.00–19.99	20.00–49.99	≥50.00	Total
0.00–0.99	30	9	7	11	4	2	63
1.00–49.99	18	9	4	15	7	1	54
50.00–99.99	6	1	2	3	1	2	15
100.00–499.99	17	2	3	4	3	2	31
≥500.00	6	6	2	3	3	2	22
Total	77	27	18	36	18	9	185

[a] Values are given for 185 children.

(308 children) and the already-assembled 150 families (185 children), but generally less than 5% for maternal dose (Web Table 3). For de novo copy-number variants, we estimate a statistical power (1-sided $\alpha = 0.05$) of 10%–33% for paternal exposure but no more than 3% for maternal exposure (Web Table 4).

There are plans to incorporate exposure measurement error into the analysis via regression calibration, possibly via more numerically intensive techniques such as Markov chain maximum likelihood (41), which takes account of the full uncertainty distribution. The errors are likely to be a mixture of Berkson error and classical error in form, with a geometric standard deviation spanning a range of at least 1–3 and a median geometric standard deviation of approximately 1.75–2.0 (27)—which is expected to increase uncertainties, and thereby reduce power, minimally.

Preliminary results

Table 1 shows, for the first 150 recruited families, the range of doses in each of the 5 exposure groups (A–E). In general, the 2 doses evaluated (DOB-51 and DOB-38) were almost identical, because only 3 of the children were conceived during the 3-month period after exposure (Table 2). The mean DOB-38 gonadal dose was estimated to be 210 mGy for fathers, with a range of 0–4,140 mGy, and 16 mGy for mothers, with a range 0–550 mGy. Table 1 shows that the means and ranges varied by exposure category, with the highest values seen in category E (high-dose emergency workers) and category C (both parents exposed).

Gonadal doses varied by exposure pathway. For external irradiation during the cleanup mission, the mean gonadal doses for 83 fathers and 27 mothers who were involved in cleanup work were estimated to be 420 mGy and 32 mGy, respectively. Doses from external irradiation during residence in Pripyat were estimated to be 3 mGy for fathers and 15 mGy for mothers. Doses incurred during residence in contaminated areas other than Pripyat were 2 mGy for fathers and 3 mGy for mothers.

A cross-classification of parental radiation doses (Table 2) shows that among the 53 fathers with the highest doses (≥100 mGy), 58% of the mothers had low doses (<5 mGy). Among mothers with higher doses (≥50 mGy), 67% of the fathers had similar doses.

Table 3 provides descriptive data on the first 150 families enrolled in the study, including the distribution of parent-offspring characteristics and responses to the questionnaire items on lifestyle and radiation exposure described above. When the study began, prevalent cancer cases were identified, but as recruitment proceeded, families with prevalent cancer cases were excluded on the basis of one of the interview questions added. Thus, for the 150 families, a cancer diagnosis was reported for 12 of the fathers, 9 of the mothers, and only 1 child.

The parents, who were in their 50s at the time of interview, were in their early 20s at the time of the 1986 Chornobyl accident and mostly in their mid- to late 20s at the time of conception. For approximately half of both mothers and fathers, the interval between exposure incurred as cleanup workers or evacuees and the time of conception was more than 5 years. Only 7% of the children were conceived during the first year after exposure.

Smoking was common among fathers (73.3%), less common among children (41.1%), and less frequent among mothers (23.3%). One-third (34%) of the fathers reported drinking alcohol once a week or more, as compared with 10% of mothers and 11% of offspring.

Just over one-third (36%) of fathers reported "ever working with radiation" (other than in relation to Chornobyl), largely in the nuclear power industry. One-fifth (20%) of parents had ever worked in a "hazardous industry," such as the military or an electrical or chemical industry.

Figure 2 shows lessons learned during the initial phase of conducting the study. Key points pertain to the identification of eligible families, recruitment, enrollment, and protocol implementation.

DISCUSSION

Herein, we describe the design and methodology for the NCI-NRCRM Study, which was initiated to investigate the transgenerational effects of parental radiation exposure in father-mother-offspring sets using high-quality biospecimens with corresponding radiation dose estimates and

Table 3. Baseline Sociodemographic and Lifestyle Characteristics and Radiation-Related Exposures of 150 Families Enrolled in a Study of Transgenerational Effects of Parental Irradiation During the Chornobyl Nuclear Accident, Ukraine, 2014–2018

Characteristic	Family Member					
	Mother ($n = 150$)		Father ($n = 150$)		Child(ren) ($n = 185$)	
	No.	%	No.	%	No.	%
Age at the time of exposure, years[a]						
<20.0	41	27.4	60	40.0	N/A	
20.0–29.9	87	58.0	79	52.7	N/A	
30.0–39.9	20	13.3	11	7.3	N/A	
≥40.0	2	1.3	0	0	N/A	
Age at the time of child's conception, years[b]						
<20.0	2	1.1	19	10.3	N/A	
20.0–29.9	116	62.7	116	62.7	N/A	
30.0–39.9	61	33.0	48	25.9	N/A	
≥40.0	6	3.2	2	1.1	N/A	
Time between exposure and conception, years[b]						
<0.25	2	1.1	1	0.5	N/A	
0.25–0.99	11	5.9	11	6.0	N/A	
1.00–1.99	26	14.1	26	14.1	N/A	
2.00–2.99	18	9.7	16	8.6	N/A	
3.00–3.99	23	12.4	24	13.0	N/A	
4.00–4.99	16	8.6	15	8.1	N/A	
5.00–5.99	9	4.9	11	6.0	N/A	
6.00–6.99	19	10.3	20	10.8	N/A	
7.00–7.99	20	10.8	18	9.7	N/A	
8.00–8.99	12	6.5	12	6.5	N/A	
9.00–9.99	12	6.5	13	7.0	N/A	
≥10.00	17	9.2	18	9.7	N/A	
Ethnicity						
Ukrainian	122	81.3	115	76.7	184	99.5
Belarussian	6	4.0	7	4.7	0	0
Russian	20	13.3	27	18.0	0	0
Other	2	1.3	1	0.7	1	0.5
Marital status						
Married	143	95.3	143	95.3	48	25.9
Never married	0	0	1	0.7	133	71.9
Widowed	1	0.7	0	0	0	0
Divorced	6	4.0	6	4.0	3	1.6
Unknown	0	0	0	0	1	0.5
Ever working with radiation						
Yes	10	6.7	54	36.0	0	0
No	140	93.3	96	64.0	185	100.0
Ever working with radiation in nuclear power industry						
Yes	4	2.7	33	22.0	0	0
No	146	97.3	117	78.0	185	100.0

Table continues

Table 3. Continued

Characteristic	Family Member					
	Mother (*n* = 150)		Father (*n* = 150)		Child(ren) (*n* = 185)	
	No.	%	No.	%	No.	%
Army service						
Yes	0	0	22	14.7	0	0
No	150	100.0	128	85.3	185	100.0
Ever working in a hazardous industry[c]						
Yes	25	16.7	32	21.3	7	3.8
No	125	83.3	118	78.7	178	96.2
Ever smoking cigarettes						
Yes	35	23.3	110	73.3	76	41.1
No	115	76.7	40	26.7	109	58.9
Duration of smoking, years						
Never smoked	114	76.0	40	26.7	109	58.9
1–4	5	3.3	9	6.0	35	18.9
5–19	18	12.0	32	21.3	39	21.1
≥20	13	8.7	69	46.0	0	0
Smoking intensity, cigarettes/day						
Never smoked	114	76.0	40	26.7	109	58.9
1–4	7	4.7	9	6.0	6	3.2
5–19	20	13.3	45	30.0	47	25.4
≥20	3	2.0	49	32.7	12	6.5
Frequency of alcohol consumption						
Never drank	26	17.3	19	12.7	26	14.1
Once a month or less	73	48.7	39	26.0	102	55.1
2–3 times per month	36	24.0	41	27.3	37	20.0
Once a week	12	8.0	31	20.7	13	7.0
Several times per week	3	2.0	18	12.0	6	3.2
Every day	0	0	2	1.3	1	0.5

Abbreviation: N/A, not applicable.

[a] Time of exposure is defined as follows: for cleanup workers, the date of the beginning of the first cleanup working mission; for residents of Pripyat, April 26, 1986; and for residents of other settlements, April 26, 1986.

[b] Values are given for 185 children.

[c] Hazardous industries were defined as those involving exposure to gasoline (petrol), organic solvents, or agricultural pesticides.

extensive phenotypic data. The study has several noteworthy aspects, including its scale. With a target of 450 families, and recruitment to date more than halfway completed (as of July 6, 2019, 283 families had been enrolled and 273 had been interviewed, including 221 families with 1 child and 52 families with 2 or more children, for a total of 329 offspring), there is adequate power to detect transgenerational radiation effects in a specific region of the genome as well as across the full genome (Web Appendix). The NRCRM Clinico-Epidemiologic Registry is a source for identification of potential family subjects, and recruitment has been highly successful. The detailed questionnaire and its quality control directives enable examination of main effects and potential interactions with variables of interest, such as age of the parents and sex of the offspring. Dose reconstruction is thorough, accounting for 3 possible pathways of exposure according to current methods, with estimates reviewed by experts in the field. The study is sufficiently powered to ensure that results could be applicable to a number of settings. The large study size and strong design, the high statistical power for de novo mutations and minisatellite mutations (Web Appendix), the collaboration with an experienced partner institute in Ukraine, the success in recruitment of family sets to date,

and the sophisticated dosimetry for reconstructing doses are all significant strengths.

Few studies have utilized genomic technologies to explore transgenerational effects of ionizing radiation at high whole genome coverage of 80× using short-read next-generational sequencing. The 2-generational study design not only will provide new insights into transgenerational effects of radiation exposure overall but also can inform issues related to paternal versus maternal exposure, although it has limited power to assess modifying effects before conception, specifically for up to 3 months preconception (Table 3). Determination of parent of origin (∼40%) of events will help evaluate relative paternal and maternal effects. A limitation of the study is that, with rare exceptions, maternal doses are lower than the paternal ones; statistical power remains high for de novo mutations (>99%) (Web Table 2) but lower for maternal genomic endpoints (<5%) (Web Tables 3 and 4). Assessment of the impact of both duration of exposure and the interval between irradiation and conception can also be investigated in the families across 2 generations, and the observations on sex differences, duration of exposure, and timing of exposure have possible implications for clinical practice as well as radiation protection.

Transgenerational effects of radiation exposure remain a serious concern. In recent surveys, nearly half of Fukushima evacuees reported anxieties about the effects of radiation on their offspring (42), an important factor in their reluctance to return home (43). Moreover, there are substantive concerns about the effect of the stress of being branded a "victim" and the associated relocation, but since we did not collect information on these issues during the interviews, we are unable to effectively investigate such established factors as glucocorticoid levels or the passage of methylation patterns through generations following stress (44, 45). The NCI-NRCRM Study, with its size, scope, and strong design and methods, will make a substantial contribution to the body of evidence on the heritable effects of moderate- and low-dose radiation exposure in humans, to our understanding of the impact of nuclear accidents, to radiation risk protection, and to the safe use of radiography in diagnosis and therapy.

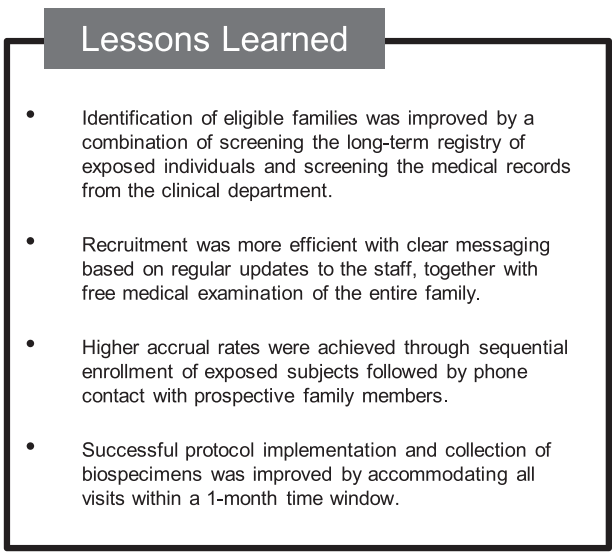

Figure 2. Lessons learned about study design methodology for family studies with past exposure.

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Lack of transgenerational effects of ionizing radiation exposure from the Chernobyl accident

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Effects of radiation exposure from the Chernobyl nuclear accident remain a topic of interest. We investigated whether children born to parents employed as cleanup workers or exposed to occupational and environmental ionizing radiation post-accident were born with more germline de novo mutations (DNMs). Whole-genome sequencing of 130 children (born 1987-2002) and their parents did not reveal an increase in the rates, distributions, or types of DNMs versus previous studies. We find no elevation in total DNMs regardless of cumulative preconception gonadal paternal (mean = 365 mGy, range = 0-4,080 mGy) or maternal (mean = 19 mGy, range = 0-550 mGy) exposure to ionizing radiation and conclude over this exposure range, evidence is lacking for a substantial effect on germline DNMs in humans, suggesting minimal impact on health of subsequent generations.

Nearly all inherited genetic variation is present in the germline DNA of at least one parent; however, a small number of transmitted variants are unique, having arisen due to random mutations in gametes (sperm and oocytes), and are known as de novo mutations (DNMs). DNMs are critical building blocks of evolution and the only class of genomic variation that has not undergone extensive evolutionary purifying selection (purging of highly deleterious but non-lethal variants), making DNMs a unique form of inherited variation different from the genetic variation investigated in mapping complex traits and diseases (*1*). DNMs have been of intense interest because of their role in human disease, particularly neurodevelopmental disorders (*2*, *3*).

Only recently has it been feasible to comprehensively investigate DNMs genome-wide at the population level in humans by whole-genome sequencing (WGS) of mother/father/child trios. Recent reports of human DNMs characterized by WGS of trios estimate between 50 and 100 new mutations arise per individual per generation (*2*, *4*–*8*), consistent with the population genetic estimate that the human mutation rate for single-nucleotide variants (SNVs) is approximately 1×10^{-8} per site per generation (*9*, *10*). The strongest predictor of DNMs per individual is paternal age at conception (*2*–*6*, *8*) with an increase of 0.64-1.51 per one-year increase in paternal age (*6*, *8*, *11*) while a maternal effect of approximately 0.35 per one-year increase in age was observed (*6*, *8*, *12*). Transgenerational studies of radiation exposure have primarily focused on disease (cancer, reproductive, and developmental) outcomes and have reported inconclusive results (*13*, *14*).

Exposure to ionizing radiation is known to increase DNA mutagenesis above background rates (*15*, *16*). Animal and cellular studies suggest high doses of ionizing radiation can lead to DNMs in offspring, particularly through double-stranded breaks (*13*, *17*). Human studies have sought a biomarker of prior radiation injury (*13*, *18*, *19*), but have examined a small number of minisatellites and microsatellites, yielding inconclusive results (*20*–*23*). A WGS study of three trios from

survivors of the atomic bomb in Nagasaki did not reveal a high load of DNMs (*20*), while a single-nucleotide polymorphism (SNP) array study of 12 families exposed to low doses of Caesium-137 from the Goiania accident in Brazil reported an increase in large de novo copy-number variants (*24*). No large comprehensive effort has explored DNMs genome-wide in children born from parents exposed to moderately high amounts of ionizing radiation yet possible genetic effects have remained a concern for radiation-exposed populations, such as the Fukushima evacuees (*25*).

Herein, we examine whether rates of germline DNMs were elevated in children born to parents exposed to ionizing radiation from the 1986 Chernobyl (Chornobyl in Ukrainian) disaster, where levels of exposure have been rigorously reconstructed and well-documented (*26*). Our study focused on children born of enlisted cleanup workers ("liquidators") and evacuees from the town of Pripyat or other settlements within the 70-km zone around Chernobyl Nuclear Power Plant in Ukraine (*27*) after the meltdown, some of whom had extremely high levels of radiation exposure and several of whom experienced acute radiation syndrome. We performed Illumina paired-end WGS (average coverage 80X), SNP microarray analysis, and relative telomere length assessment on available samples from 130 children from 105 mother-father pairs. The parents had varying combinations of elevated gonadal ionizing radiation exposure from the accident (tables S1 to S3), and included a combination of exposed fathers, exposed mothers, both parents exposed and neither parent exposed (*27*). Fathers' cumulative gonadal ionizing radiation dose ("dose") at conception ranged from 0 to 4,080 mGy (mean = 365, median = 29, standard deviation (sd) = 685) with 17 exposed to >1000 mGy, whereas mothers' dose ranged from 0 to 550 mGy (mean = 19, median = 2.1, sd = 72) with only 2 exposed to >500 mGy (table S3). Paternal age at exposure ranged from 12-41 years, and maternal from 10-33 years. Paternal mean age at conception was 29 (range = 18-52, sd = 5.7) while maternal mean age was 27 (range = 18-39, sd = 5.2). 58 (45%) children were female and 72 (55%) were male. Children born 46 or more weeks after the Chernobyl accident were included; birth years were between 1987 and 2002 (52% prior to 1992). There were 23 families with two or three siblings analyzed, but no twins. Principal component analysis (PCA) revealed nearly all parents shared common Eastern European heritage (fig. S1), and pairwise identity-by-descent analysis revealed four first-degree relative sets among the parents.

Two modified MIE filtering strategies were applied for post-variant calling and detection of Mendelian inconsistency error (MIE) determination (*8*, *28*). All putative DNMs passing filtering criteria were examined manually, and the total number of DNMs were tallied for each the following classes, reflecting distinct mutational mechanisms: a) single-nucleotide variants (SNVs), b) small insertions/deletions (indels), c) complex variants (variants that arose from a complicated mutational event), and d) SNV/indel clusters, which are two or more variants that occur closer than expected by chance (as defined by Jónsson *et al.* (*6*)) (Table 1). Each instance of a complex variant or SNV/indel cluster was counted once, effectively assuming that clustered changes occurred together during one replication cycle. Length variants at microsatellite loci were examined separately since they have been previously reported as a potentially important class of mutation following radiation exposure (*21*, *22*, *29–31*). While DNMs involving microsatellite loci were analyzed separately, they were tallied overall with indels. All variants are provided in table S1.

There was no evidence for a relationship between the total number of DNMs and preconception ionizing radiation dose (cumulative estimated gonadal dose at 38 weeks before birth) for maternal (−0.02 DNM per mGy, 95% CI: −0.04-0.007, p = 0.17) or paternal (−0.0007 DNM per mGy, 95% CI: −0.003-0.002, p = 0.56) exposures (Table 2 and fig. S2). In an analysis restricted to DNMs with known parent-of-origin (42%; Table 1), no effect of radiation was observed (table S4) whereas the effect of parental age remained robust; the parent-of-origin point estimates for paternal and maternal age effects were 0.71 and 0.28, respectively. Further investigation did not reveal evidence for an effect of preconception dose for any individual class of DNMs evaluated (table S5). Sensitivity analysis conducted with doses truncated at 1000 mGy or log transformed (ln(1+dose(mGy))) did not reveal an impact of maternal and paternal dose modeling on association with DNMs (Table 3). We further investigated categorical dose levels and found no increase in DNMs for any dose category, even 1000+mGy paternal dose (table S6). No effect of time since exposure was observed between parental preconception ionizing radiation exposure and DNM count for children born in the years immediately following the Chernobyl accident (Fig. 1). Moreover, when restricting to SNVs, there was no difference in the distribution of nucleotide substitutions based on quartile of maternal and paternal dose (fig. S3). Furthermore, the rates and types (molecular spectra) of DNMs observed in the current study were similar to those observed in prior studies conducted in general populations (Fig. 2 and fig. S4) (*2–4*, *6*, *8*).

Since lifestyle exposures such as smoking have been associated with alterations of DNA (for example, mosaic loss of Y chromosome (*32*)), we also investigated possible effects of prenatal parental alcohol consumption and smoking on DNMs. We observed no association between the number of DNMs and either paternal tobacco smoking at conception (6.78, 95% CI = −16.62-14.87, p = 0.13, Table 2 and Fig. 1) or maternal tobacco smoking at conception (23.38, 95% CI = −2.00-48.77, p = 0.07, Table 2 and Fig. 1). Similarly, no effect

was observed for increasing levels of paternal (p = 0.12) or maternal (p = 0.12) preconception alcohol consumption. In addition, sequencing batch had no impact on the number of DNMs (4.45, 95% CI = −5.07-13.97, p = 0.34).

Relative telomere length was measured by qPCR (*33*) in participants to investigate the potential transgenerational impact of parental ionizing radiation on leukocyte telomere length in children. As expected, an overall relationship was observed between increasing age at blood draw and shorter relative telomere length due to age-related telomere length attrition ($p = 4.49\times10^{-19}$, fig. S5). We did not observe an effect of paternal or maternal age at conception on relative telomere length in adult children (p = 0.95 and 0.06, respectively; table S7). While our analysis did not find evidence for an effect of total paternal preconception ionizing radiation exposure on relative leukocyte telomere length (p = 0.88), we did observe a possible effect of total maternal preconception exposure that requires confirmation (-2.75×10^{-4}, 95% CI = -5.20×10^{-4} - -2.90×10^{-5}, p = 0.03; table S7). There was no evidence for a transgenerational effect of paternal or maternal smoking on child's telomere length (p = 0.91 and 0.22, respectively, table S7).

Although it is reassuring that no transgenerational effects of ionizing radiation were observed in adult children of Chernobyl cleanup workers and evacuees in the current study, additional investigation is needed to address the effects of acute high-dose parental gonadal exposure closer to conception. The upper 95% confidence bound suggests the largest effect consistent with our data is <1 DNM per 100 mGy from paternal or maternal exposure (Table 3 and tables S8 and S9). Previously, Dubrova *et al.* (*22*, *29*) reported a two-fold increase in mini-satellite mutations in children born to parents living in a highly exposed region of Belarus. Weinberg *et al.* (*34*) reported an increase in the mutation rate at microsatellite loci among children born to cleanup workers. Subsequent small studies have not reported an increased mini-satellite or microsatellite mutation rate in children of cleanup workers, including those with low doses (0.09-0.23 Gy) (*21*, *30*, *35*) or in children of the atomic-bomb survivors of Hiroshima or Nagasaki (*31*).

Our study evaluated peripheral blood from adult children conceived months or years after the Chernobyl accident, which limited the ability to assess exposure closer to conception; however, there was no evidence of notable differences in DNMs in children born the following year (1987). Since these families were recruited several decades after the accident, we acknowledge potential survivor bias among sampled children, although this is unlikely since there is no consistent demonstration in humans of sustained clinical effects of preconception ionizing radiation exposure (*36*). The number of parental gonadal radiation-induced double strand breaks could be fewer than anticipated based on animal data, which often assesses acute exposure (as a single burst) at higher doses (2-4 Gy; (*13*, *37*)). Doses to the Chernobyl liquidators were mostly lower and exposure was fractionated over an extended period of time, which could have decreased the probability of gonadal DNM events. Moreover, it is plausible that the balance between radiation-induced mutations and accurate repair over time favored the latter. Additionally, there could have been a loss of power due to dose errors. Further human studies are needed to investigate the frequency of radiation-induced mutations and the subsequent response to address both the accuracy and efficiency of DNA repair. In a genomic landscape analysis of 440 cases of papillary thyroid cancer following the Chernobyl accident, increased radiation exposure was associated with a shift in tumor drivers from point mutations to small indels and non-homologous end joining events underlying fusions and other structural variants (*38*). Notably, there was no evidence of a radiation-specific single base substitution signature, gene expression pattern or methylation profile in cases of thyroid cancer with comparable radiation exposure history; instead, these were strongly associated with the tumor driver.

The rate, class distribution, and SNV type distribution of DNMs in adult children born to parents exposed to ionizing radiation, specifically of the type and amount relevant to Chernobyl cleanup workers and evacuees, are comparable to those reported in the general population. No effect of radiation on the specific classes of DNMs (SNVs, indels, complex variants, or clusters) was observed (table S5). Paternal age remains the strongest contributor to DNMs, although with maternal age DNMs also increase albeit with lower magnitude (Table 2 and table S4; (*12*)). Our study sample did not include mothers with high exposure (>1 Gy), but lower maternal dose was not associated with elevated DNMs, consistent with animal studies (*13*). Furthermore, our analysis of 130 adult children from 105 couples using 80X coverage of short-read technology suggests that if such effects on human germline DNA occur, they are uncommon or of small magnitude. This is one of the first studies to systematically evaluate alterations in human mutation rates in response to a man-made disaster, such as accidental radiation exposure. Investigation of trios drawn from survivors of the Hiroshima atomic bomb could shed further light on this public health question. In conclusion, children of individuals exposed to either occupational or environmental radiation do not appear to experience elevated rates of DNMs from their parents' exposure. Thus, our study does not provide support for a transgenerational effect of ionizing radiation on germline DNA in humans.

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MSMuTect, MSMutSig, MSIdetect, POLYSOLVER and TensorQTL. G.G. is a founder, consultant and holds privately held equity in Scorpion Therapeutics. All other authors declare no competing interests. **Data and materials availability:** Molecular data are available from the Genomic Data Commons: https://gdc.cancer.gov/about-data/publications/TRIO-CRU-2021, accessed through the database of Genotypes and Phenotypes (dbGaP, accession phs001163.v1.p1; www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001163.v1.p1). The MIE filtering pipeline code can be found at https://github.com/NCI-CGR/ChernobylDNMCalling.

SUPPLEMENTARY MATERIALS

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Materials and Methods
Figs. S1 to S7
Tables S1 to S10
References (*40*–*47*)
MDAR Reproducibility Checklist

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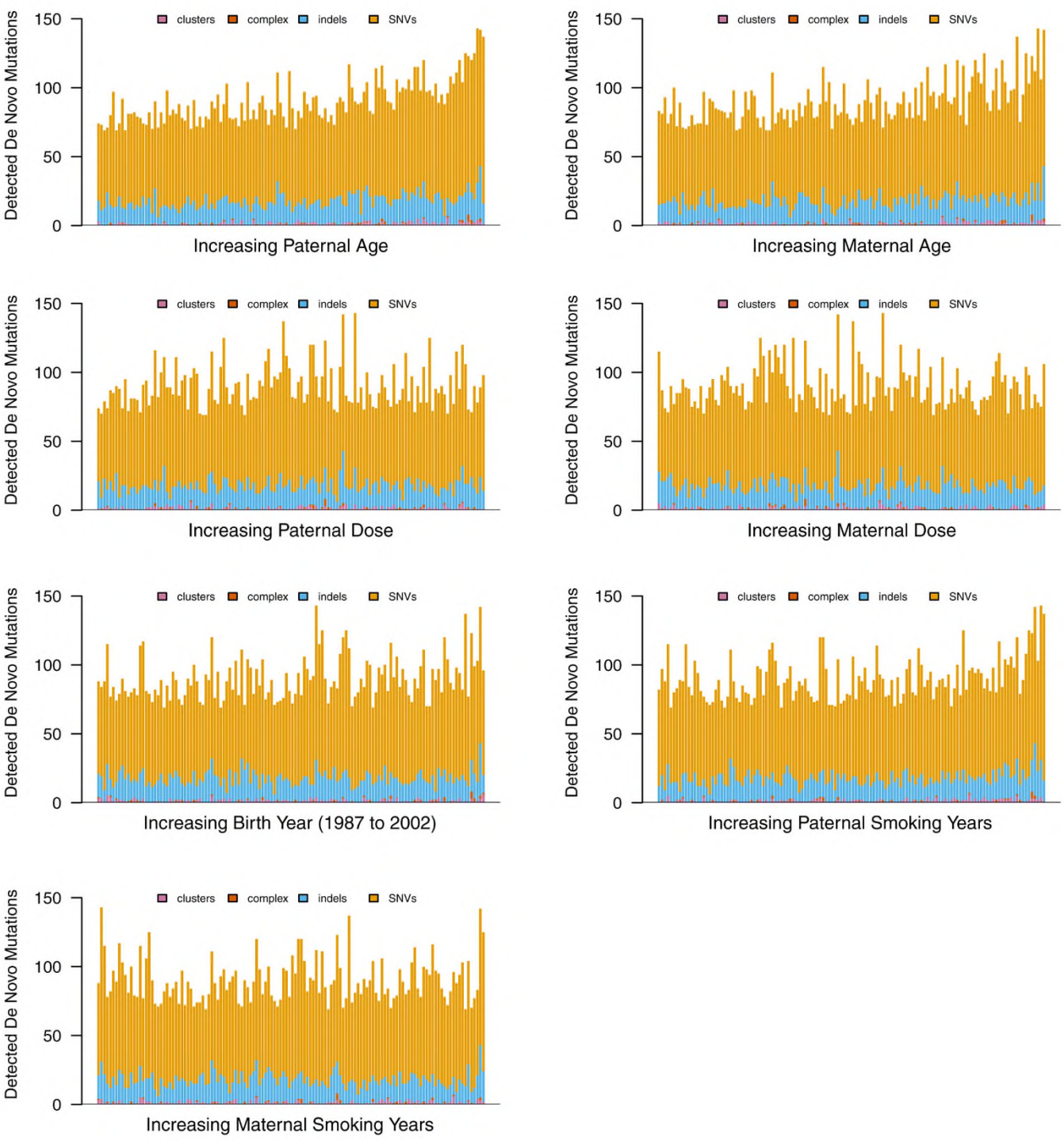

Fig. 1. Detected DNMs per genome based on distributions of parental age at conception. Analyses are presented by increasing paternal and maternal age at conception, paternal and maternal dose, birth year of child, and paternal and maternal smoking at conception. All plots are univariate and do not account for other potentially correlated variables (for example, maternal age does not account for high correlation with paternal age).

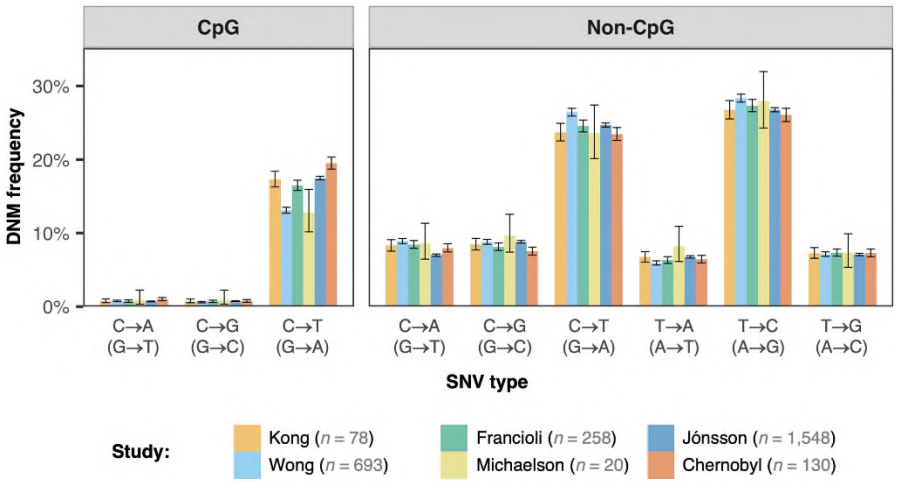

Fig. 2. Distribution of de novo SNVs by type of nucleotide change across six studies. *n* = number of children sequenced (adapted from (*39*)). Liftover was used to convert coordinates to hg38 for all studies and the reference for CpG sites were defined with respect to that reference sequence. Only autosomes were included. Error bars show binomial 95% confidence intervals. Studies included Kong (*2*); Wong (*8*); Francioli (*4*); Michaelson (*3*); Jónsson (*6*); and Chernobyl (present study).

Table 1. Distribution of detected DNMs in the Chernobyl Trios. Results reported as events per diploid genome per generation and proportion phased to paternal and maternal haplotypes. Microsatellites are a smaller group within indels; the mean microsatellite count (5.62) is a part of the total mean indel count (16.18).

	Mean	Median	Range	Standard Deviation
Number of Clusters	1.39	1	0-6	1.34
Number of Complex	0.38	0	0-5	0.77
Number of Indels	16.18	15	5-38	5.10
Number of Microsatellites	5.62	5.5	0-13	2.49
Number of SNVs	72.22	69.5	47-121	13.36
Total Number of DNMs	90.17	88	69-143	15.94
Phased to Paternal Haplotype	29.33	29	12-53	7.08
Phased to Maternal Haplotype	8.61	8	2-20	4.07
Proportion Phased	42.1%	41.5%	27.6-55.8%	6.3%

Table 2. Associations of age at conception, cumulative ionizing radiation dose, and smoking history with DNM count. Multiple regression estimates for age and radiation dose are average changes in total DNMs per one unit increase in the respective variables. Smoking estimates are in comparison to never smokers. The model was additionally adjusted by sequencing batch.

	Estimate	95% Confidence Interval	P-value
Age at conception			
Maternal age	0.46	−0.02, 0.93	0.06
Paternal age	1.94	1.51, 2.36	3.65×10^{-15}
Cumulative radiation dose (/mGy)			
Maternal dose	−0.02	−0.04, 0.007	0.17
Paternal dose	−0.0007	−0.003, 0.002	0.56
Smoking history			
Maternal former smoker	−4.13	−10.74, 2.49	0.22
Maternal current smoker	5.31	−0.18, 10.81	0.06
Paternal former smoker	0.91	−5.16, 6.97	0.77
Paternal current smoker	2.91	−0.93, 6.75	0.14

Table 3. Sensitivity analyses of the impact of maternal and paternal cumulative radiation dose modeling on association with DNMs. All models are adjusted for sequencing batch, maternal and paternal age, and maternal and paternal smoking status. Additional analyses by dose categories are in table S6.

	Estimate	95% CI	P-value
Cumulative radiation dose (/mGy)			
Maternal dose	−0.02	−0.04, 0.007	0.17
Paternal dose	−0.0007	−0.003, 0.002	0.56
Cumulative radiation dose truncated at 1,000 (/mGy)			
Maternal dose	−0.02	−0.04, 0.009	0.21
Paternal dose	−0.003	−0.008, 0.001	0.17
Cumulative log radiation dose (/ln(1+mGy))			
Maternal dose	−0.87	−2.12, 0.39	0.18
Paternal dose	−0.37	−1.07, 0.33	0.30

Science

Lack of transgenerational effects of ionizing radiation exposure from the Chernobyl accident

Meredith Yeager, Mitchell J. Machiela, Prachi Kothiyal, Michael Dean, Clara Bodelon, Shalabh Suman, Mingyi Wang, Lisa Mirabello, Chase W. Nelson, Weiyin Zhou, Cameron Palmer, Bari Ballew, Leandro M. Colli, Neal D. Freedman, Casey Dagnall, Amy Hutchinson, Vibha Vij, Yosi Maruvka, Maureen Hatch, Iryna Illienko, Yuri Belayev, Nori Nakamura, Vadim Chumak, Elena Bakhanova, David Belyi, Victor Kryuchkov, Ivan Golovanov, Natalia Gudzenko, Elizabeth K. Cahoon, Paul Albert, Vladimir Drozdovitch, Mark P. Little, Kiyohiko Mabuchi, Chip Stewart, Gad Getz, Dimitry Bazyka, Amy Berrington de Gonzalez and Stephen J. Chanock

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7. СУПУТНІ ПОГЛИБЛЕНІ ДОСЛІДЖЕННЯ, ІНІЦІЙОВАНІ У СПОСТЕРЕЖУВАНИХ КОГОРТАХ

Продемонстрований дозо залежний надлишок виникнення ХЛЛ спонукав до дослідження можливих дозо залежних клінічних особливостей перебігу цього захворювання у зв'язку з експозицією до іонізуючого випромінювання, а також ймовірних генетичних ушкоджень, які могли сприяти підвищеному ризику реалізації цієї форми лейкемії у ліквідаторів.

В **підрозділі 7.1** представлено результати дослідження геномної характеристики ХЛЛ у учасників ЛНА.

Для дослідження з використанням CNA (аналізу числа копій), числа мутацій було сформовано спостережувані групи, які включали (1) 16 випадків ХЛЛ серед учасників ЛНА; (2) 28 випадків ХЛЛ серед неопроміненого населення України, відповідної структури за гендерно-віковими характеристиками і (3) 100 випадків ХЛЛ, зареєстрованих в Dana Farber Cancer Institute (DFCI), США. Серед хворих ліквідаторів не було встановлено збільшеного числа мутацій в ХЛЛ–асоційованих генах, порівняно із неопроміненими особами. Дослідження показало збільшення довжини теломер в пухлинних клітинах і мутації в генах підтримання теломер, які можуть відігравати певну роль в генезисі радіаційно-асоційованого захворювання на ХЛЛ, яке потребує подальшого вивчення. Українські пацієнти з ХЛЛ без анамнезу радіаційного опромінення мали соматичну геномну архітектуру, подібну до західних хворих на ХЛЛ. Наш аналіз хворих на ХЛЛ під впливом радіації внаслідок ЛНА, визначає можливість, що доза на червоний кістковий мозок корелює зі збільшенням ураження генетичних драйверів.

В дослідження клінічних особливостей ХЛЛ у учасників ЛНА **(підрозділ 7.2)** було включено 79 випадків із верифікованим діагнозом і реконструйованою дозою зовнішнього опромінення на червоний кістковий

мозок. Діапазон отриманих доз опромінення становив від 0 до 1 536.2 мГр із медіанним значенням 22.6 мГр. Розподіл випадків, згідно рівня дози опромінення, як і всіх ліквідаторів в цілому, був дуже зміщеним в бік низьких значень таким чином, що для 56 (70.9%) випадків ХЛЛ значення було нижчим за 100 мГр. Медіана віку на момент експозиції була 45 років і на момент встановлення діагнозу 57 років. Не було визначено залежності латентного періоду захворювання та клінічних особливостей перебігу захворювання від отриманої дози опромінення. В той же час, аналіз даних показав, що латентний період був суттєво коротшим у осіб, опромінених у більш літньому віці, у осіб, які палять, а також які були старшими за віком при встановленні діагнозу ($p < 0.05$). Достовірно вищим був ризик смерті у осіб, опромінених у дозі, вищій за 22 mGy, порівняно із опроміненими в дозі, нижчій за цей рівень. Виживаність була коротшою серед випадків ХЛЛ, опромінених в більш молодому віці та вищим рівнем лімфоцитозу. Щоб посилити потужність оцінок і підтвердити визначені ефекти, необхідним є продовження досліджень із включенням більшого числа випадків.

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Genomic characterization of chronic lymphocytic leukemia (CLL) in radiation-exposed Chornobyl cleanup workers

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Abstract

Background: Chronic lymphocytic leukemia (CLL) was the predominant leukemia in a recent study of Chornobyl cleanup workers from Ukraine exposed to radiation (UR-CLL). Radiation risks of CLL significantly increased with increasing bone marrow radiation doses. Current analysis aimed to clarify whether the increased risks were due to radiation or to genetic mutations in the Ukrainian population.

Methods: A detailed characterization of the genomic landscape was performed in a unique sample of 16 UR-CLL patients and age- and sex-matched unexposed general population Ukrainian-CLL (UN-CLL) and Western-CLL (W-CLL) patients ($n = 28$ and 100, respectively).

Results: Mutations in telomere-maintenance pathway genes *POT1* and *ATM* were more frequent in UR-CLL compared to UN-CLL and W-CLL (both $p < 0.05$). No significant enrichment in copy-number abnormalities at del13q14, del11q, del17p or trisomy12 was identified in UR-CLL compared to other groups. Type of work performed in the Chornobyl zone, age at exposure and at diagnosis, calendar time, and Rai stage were significant predictors of total genetic lesions (all $p < 0.05$). Tumor telomere length was significantly longer in UR-CLL than in UN-CLL ($p = 0.009$) and was associated with the *POT1* mutation and survival.

Conclusions: No significant enrichment in copy-number abnormalities at CLL-associated genes was identified in UR-CLL compared to other groups. The novel associations between radiation exposure, telomere maintenance and CLL prognosis identified in this unique case series provide suggestive, though limited data and merit further investigation.

Keywords: Ionizing radiation, Chronic lymphocytic leukemia, Mutation, Telomere, Chernobyl, Chornobyl

Background

Chronic lymphocytic leukemia (CLL) is the predominant type of leukemia among males in Western populations (30–40%) [1] and in Ukraine (> 50% in those 44 years and older) [2]. Validated CLL risk factors include male sex, longer telomere length, and several inherited genetic polymorphisms [3]. The clinical course of the disease is very heterogeneous, ranging from indolent to aggressive and rapidly progressive. Advances in microarray and sequencing technologies have identified genetic biomarkers of CLL as recurrent copy number abnormalities (CNAs), including del13q14, del11q22–23, del17p, trisomy-12, and frequent point mutations in *SF3B1*, *NOTCH1*, *BIRC3* and other genes [4]. Clinical characterization of these mutations has identified del17p, *TP53,* and *BIRC3* as markers of high-risk CLL, and *NOTCH1* and/or *SF3B1* as markers of intermediate risk [4].

It has been known, since the early 1950's from the Hiroshima and Nagasaki atomic bomb (A-bomb)

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survivors' study, that radiation exposure may induce most types of leukemia [5]. However, it generally has been accepted that radiation does not induce CLL. Until recently, the majority of epidemiological studies of occupational, environmental, or therapeutic exposure to radiation reported no excess risk of CLL [5]. Evidence suggests that mortality-based studies could underestimate, possibly substantially, CLL occurrence due to its benign clinical course, thus incidence studies are needed to characterize risks of low-dose radiation exposures [6]. Contrary to previous findings, recent incidence studies from our group [7, 8], other groups studying occupationally exposed radiation workers [9, 10], as well as the most recent update of the A-bomb incidence follow-up study [11], albeit based on a small number (12) of cases, reported significantly increased radiation risks of CLL.

In our recent study of the 1986 Chornobyl (Chernobyl) nuclear accident, CLL was the predominant leukemia in Ukrainian cleanup workers [7]. We reported significantly increased risks of CLL with increasing bone marrow radiation doses, which could not be explained by differences in lifestyle or environmental exposures [12]. Similar but statistically non-significant findings were observed for Chornobyl cleanup workers from Belarus, Russia and the Baltic countries [10]. Risk of CLL in Russian Chornobyl cleanup workers was not elevated [13], but questions have been raised about this analysis based on the official reported doses and the Chornobyl Registry-based leukemia diagnoses. Overall, there is now an emerging consensus on the role of ionizing radiation (IR) exposure in the etiology of CLL, but the magnitude of risks remains unknown. Further studies with large sample size of incident cases are warranted to understand the effect of IR on CLL.

One of the main hypothesized mechanisms underlying radiation-associated CLL is the absorption of energy from IR by genetic material leading to genomic instability [14]. Although studies have reported deregulated gene expression in CLL specimens obtained in the post-Chornobyl period [15], genetic characterization of Chornobyl-associated CLL has not been previously performed. Chornobyl cleanup workers present a unique opportunity to study the relationship between IR exposure and the genomic landscape of CLL after radiation. To better understand the genetic architecture of radiation-associated CLL, we performed comparative genomic analyses of Ukrainian Chornobyl cleanup workers exposed to IR (UR-CLL) with Ukrainian non-irradiated patients (UN-CLL) and Western patients (W-CLL). Although the UR-CLL sample is small, this is a unique series of confirmed CLL cases among Chornobyl cleanup workers with individual radiation bone marrow doses, confounder data and biological specimens. To our knowledge, this is the first such study of CLL cases after confirmed radiation exposures.

Methods

Patient recruitment

Cases of CLL among Chornobyl cleanup workers were obtained from the Ukrainian-American Study of Leukemia and Related Disorders among Chornobyl Cleanup Workers from Ukraine [7]. Data on patient characteristics and estimated doses were imported from the original study [7]. Briefly, we previously conducted a case-control study nested in a cohort of 110,645 male Ukrainian workers who were 20–60 years of age during cleanup activities in 1986–1990 after the Chornobyl nuclear power plant accident and who were registered in the Chornobyl State Registry of Ukraine (SRU) before 1992 and resided in Kyiv City, or in any one of five study areas. CLL cases diagnosed in the cohort during 20 years of follow-up (1986–2006) were pathologically confirmed by the International Hematology Panel consisting of five hematologists/ hematopathologists [16]. Bone marrow aspirates/ biopsy slides and/or peripheral blood smears were available for 70% of 79 confirmed CLL cases (UR-CLL) with estimated bone marrow doses. Only 16 cases had sufficient DNA for targeted next-generation sequencing (≥100 ng).

Study samples for unexposed Ukrainian CLL (UN-CLL) cases were from the patients treated at the National Research Center for Radiation Medicine (NRCRM) in Kyiv, Ukraine during 2002–2014. CLL diagnoses were confirmed by flow cytometry. From 119 available samples, we randomly selected males of comparable age and matched them to Chornobyl CLL cases in a ratio of 2:1. The final sample included 28 samples with sufficient DNA for targeted sequencing. An additional set of Western CLL (W-CLL) patients included 100 non-overlapping patients from the Dana Farber Cancer Institute (DFCI). To compare frequency of gene mutations in Ukrainian and Western CLL cases, exome sequencing data from DFCI patients was downloaded from dbGAP (phs000435.v2.p1).

Patient characteristics

The following variables were examined for UR-CLL: the latent period (interval of time in years between the date of first exposure and the date of diagnosis of CLL)[1]; type of work performed in the 30-km Chornobyl zone (early responders, military personnel, professional nuclear power workers, other); calendar year of CLL diagnosis; time since first exposure; age at first exposure; age at diagnosis; average frequency of visits to the doctor prior to CLL diagnosis (zero, once every 2 years, more than once every 2 years)[2]; and smoking and alcohol consumption.

DNA extraction and targeted sequencing

Blood smears for UN-CLL and UR-CLL cases were verified by study hematologists. Smears were scraped with

scalpels (Miltex Inc., York, PA, USA) and DNA was extracted using QIAGEN QIAamp DNA Mini Kits (QIAGEN Inc., Valencia, CA, USA) as per manufacturer's instructions. The purity of the slides was ascertained by determining the % of blasts. The average normal cell contamination was estimated at 15% for UR-CLL and UN-CLL slides. DNA concentration and quality were estimated by picoGreen mitochondrial DNA stain (Life Technologies, Carlsbad, CA, USA, Cat # P11495). CLL cases – 16 UR-CLL and 28 UN-CLL – were selected for deep-sequencing of cancer-relevant genes to discover novel driver mutations. All UR-CLL and UN-CLL specimens were confirmed to be pre-therapy to eliminate any therapy-induced effect.

For targeted deep sequencing (TDS), SeqCap EZ Exome Probes v3.0 (Roche Sequencing Solutions, Madison, WI, USA) were used to capture exonic regions of 538 genes included in the "UCSF500 Cancer Gene Panel" (Additional file 1: Table S1). Paired-end libraries were generated as per KAPA DNA Library Kits (Kapa Biosystems, Wilmington, MA, USA). DNA samples were barcoded and pooled for multiplexed sequencing on the Illumina HiSeq 2500 platform, which was run in Rapid run mode to obtain 130 million reads per lane. Sixteen samples were multiplexed with Illumina indexes and run per lane. On average, 80% of reads were retained after duplicate filtering, less than 3% were unmappable, and the remaining 17% of the reads were mapped to off-target regions. About 70% of the reads were mapped to target and near target areas of the bait.

Raw primary sequence data (.bam files) for W-CLL cases were re-aligned and mutations were called within the same genomic-capture regions as for the UCSF500 Cancer Gene Panel.

For data analysis, initial alignment of paired-end sequencing reads to the human reference genome (UCSC version hg19) was performed using the Burrows-Wheeler Aligner (BWA version 0.7.10-r789), with reads sorted by position and converted to compressed BAM format using SAM tools. Likely PCR and optical duplicate read pairs were marked using Picard (version 1.97(1504)). Insertion and deletion (INDEL) realignment and recalibration were carried out using the Genome Analysis Toolkit (GATK) (http://www.broadinstitute.org/gsa/wiki/index.php/The_Genome_Analysis_Toolkit). Single nucleotide variants (SNVs) and small sequence INDELs were called in each sample using the GATK command "Unified Genotyper", with variant calls stored in VCF files.

Variant calls with total read depth less than 10X were excluded from further analysis for the lack of confidence in true variant calling. In the absence of matched normal sample from each tumor, to exclude likely germline polymorphisms we filtered out variants present in dbSNP or with a minor allele frequency > 0.01% in the Exome Aggregation Consortium (ExAC) Database. Coding variants predicted to affect protein sequence (e.g., nonsynonymous, stop gain, splicing) were analyzed further. To predict deleterious effects of variants, we used Polyphen, SIFT and Combined Annotation Dependent Depletion (CADD) tool version 1.3 (http://cadd.gs.washington.edu/score), which integrates information from multiple functional annotation tools into a single score. Finally, nonsynonymous variants of significant interest were visually inspected using the Integrated Genomics Viewer (http://software.broadinstitute.org/software/igv/).

Copy number analysis

CNAs were analyzed using CNVkit [17] and off-target reads from the target area with capture probes. CNVkit was run with default parameters and female genome as reference. A threshold of 0.3 was applied to identify the signals for amplification and deletions of the genomic segments.

Mutation and CNA prevalence calculation

Mutation and CNA prevalence was calculated as percent of cases harboring nonsynonymous mutations or copy number changes in a specific gene within a particular sample.

Telomere length estimation

The telomere length was estimated by using off-target reads mapping to TTAGGG telomeric repeats, which has been shown to correlate with Southern blot measurements of the mean length of terminal restriction fragments (mTRFs) [18].

NMF signature analysis

A non-negative matrix factorization (NMF) [19] was used to identify a radiation-associated mutational signature in exposed and unexposed Ukrainian CLL patients.

Bone marrow dose estimation for exposed CLL cases (UR-CLL)

A time-and-motion method of retrospective dose reconstruction in cleanup workers, known as RADRUE, was developed for the study of cleanup workers from Ukraine [20, 21] and for a similar study conducted in Belarus, Russia, and Baltic countries [10] by an international group of scientists including experts from Belarus, France, Russia, the United States, and Ukraine. The method used combined data on work history from dosimetric questionnaires with field radioactivity measurements to estimate individual bone marrow doses for all study subjects. In-person interviews were conducted by trained interviewers and included questions concerning locations of work and residence while in the 30-km exclusion zone around the Chornobyl nuclear power plant, types of work, transportation routes, and corresponding dates. For deceased CLL cases, proxy interviews were conducted with next-of kin for demographic and medical information and with co-

workers for work histories in the 30-km exclusion zone [21]. Additional validation studies have shown that bone marrow radiation dose estimates based on information from proxies were comparable to those based on direct interviews [22].

Statistical methods

All analyses relied on cumulative radiation doses derived as the sums of the arithmetic means of the annual 1986–1990 bone marrow doses estimated by generating 10,000 realizations of dose predictions from the RADRUE method as described above.

Univariate tests of normally distributed continuous variables were performed using one-way analysis of variance (ANOVA), and on non-normally distributed variables using a Wilcoxon– Mann–Whitney test. Additional multivariate analyses were conducted using Poisson regression for genetic lesions, total number of genetic lesions and mutations and telomere length, and using logistic regression for *POT1* mutations, and included categorical as well as continuous predictors.

All p-values presented were two-sided. The best fitting models were chosen by using the likelihood ratio test and Akaike Information Criterion. All analyses were conducted using the SAS 9.4 software (SAS Institute, Cary, NC, USA).

Results

This analysis is based on the 16 cases who had sufficient DNA for targeted next-generation sequencing drawn from the parent study of 79 CLL cases from the Ukrainian-American Study of Leukemia and Related Disorders among Chornobyl Cleanup Workers from Ukraine [7]. Selected cases did not differ from all cases in terms of age at first exposure, age at CLL diagnosis or radiation dose (all $p > 0.1$, not shown).

UR-CLL and UN-CLL samples were sequenced to ~450X depth and compared to W-CLL. Total numbers of nonsynonymous point mutations across the 538 cancer-relevant genes were comparable in UR-CLL (range 2–12, median 8), UN-CLL (range 2–12, median 8), and W-CLL (range 2–11, median 8) samples. CADD Phred scores indicated no statistically significant difference in deleteriousness of detected mutations across the three groups.

We further analyzed the correlation of genetic lesions (total number of mutations + CNAs) with several clinical variables (Table 1) and bone marrow radiation dose (median: 40.56 milligray (mGy); range: 0.24–1536.24 mGy). The type of work performed in the 30-km Chornobyl zone, age at first exposure, age at diagnosis, calendar time and Rai stage of CLL were identified as significant predictors of genetic lesions (all $p < 0.05$), together explaining 20% of their variability (combined pseudo$R^2 = 0.20$). Adjusting for all other factors, Chornobyl CLL patients who had more advanced stage at diagnosis (Rai stage ≥2) had a two-fold higher predicted number of total lesions compared to those diagnosed at a less advanced stage.

We compared the prevalence of putative CLL driver mutations across three samples, and *NOTCH1* was the most frequently mutated gene overall and was mutated at similar frequencies across the three samples (Fig. 1a). *POT1* was the most frequently mutated gene in UR-CLL (25%), followed by *NOTCH1, RB1 (*19% each), *ATM, APC, MED12, SF3B1*, and *KMT2C* (13% each) (Fig. 1a and Additional file 1: Table S2). The most common CNAs identified in UR-CLL were del13q14 and del11q (12% each) (Additional file 1: Table S3). No statistically significant differences were identified in frequencies of CNAs between UR-CLL, UN-CLL and W-CLL.

To further delineate genomic differences between radiation-associated CLL and idiopathic CLL, an NMF approach [19] was applied. UN-CLL tumors were enriched for mutations in genes with roles in epigenetic regulation (*EP300*, *ARID1B*, *ZMYM3*, *KMT2C*) and the Ras/MAPK signaling pathway (*FLT4*, *MET*, *EPHA7*, *MAP3K1*), consistent with previous studies (Fig. 1b) [23]. We searched for a potential radiation-associated mutational signature in UR-CLL, but a specific pattern of preferred nucleotide substitutions could not be resolved. Next, we performed pathway analyses and identified mutations in telomere-maintenance pathway genes to be enriched in UR-CLL. We observed a significantly higher frequency of *POT1* mutations in UR-CLL compared to both the UN-CLL and W-CLL cases ($p = 0.03$ and 0.009, respectively). Further, recurrent mutations were found in *ATM, RB1*, and *MED12* in UR-CLL (Fig. 1b). All 4 *POT1* mutations detected in UR-CLL were localized to OB-fold domains 1 & 2 (Fig. 2a), while recurrent *ATM* mutations were localized to other functional domains (Fig. 2b).

Since *POT1* haploin sufficiency has been reported to cause telomere elongation in CLL and glioma [24], we estimated telomere length via telseq [18] and identified a significantly longer age-adjusted mean telomere length in UR-CLL tumors compared with UN-CLL (Table 1 and $p = 0.009$ in Fig. 2c).

We further analyzed telomere length correlation with other covariates and identified lifestyle factors such as alcohol consumption, smoking and type of cleanup work performed in the Chornobyl zone as significant predictors of tumor telomere length in UR-CLL (combined $R^2 = 0.63$). In a combined analysis of telomere length among UR-CLL and UN-CLL groups, age was not a predictor of tumor telomere length ($p = 0.17$) whereas exposure to radiation was a significant and strong predictor (1.59 unit increase in length due to radiation (95% confidence interval: 0.64, 2.55, $p < 0.01$)). In total, IR explained 20% of the variability in telomere length. As *POT1* and *MED12* mutations have been previously

Table 1 Characteristics of Ukrainian CLL cases

Variable	Exposed (UR-CLL)[a]	Unexposed (UN-CLL)[b]
Cases, N	16	28
Age at diagnosis, median (range), years	61 (49–78)	58 (41–76)
Sex	Male	Male
Diagnosis year, range	1986–2006	2002–2014
Blood count, median (range), 10 × 9 per mL	13 (2–55)	54 (16–122)
Rai stage, n (%)		NaN[c]
0	1 (6)	
1	3 (19)	
2	9 (56)	
3	3 (19)	
Smoking history, n (%)		NaN[c]
never or former	9 (56)	
less than 20 cigarettes/day	5 (31)	
20 or more cigarettes/day	2 (13)	
Alcohol consumption		NaN[c]
never	4 (25)	
no more than 2–3 times a month	7 (44)	
once a week or more	5 (31)	
Bone marrow radiation dose, median (range), milligray (mGy)	40.56 (0.24–1536.24)	NA[d]
POT1 mutation, n (%)	4 (25)	0 (0)
Telomere length, median (range), kilobytes (kb)	1.58 (0.12–9.06)	0.30 (0.09–2.47)
Survival after diagnosis, median (range), years	4 (1–18)	NaN[c]

Based on 15 cases who have died by the end of follow-up
[a]CLL cases in Chornobyl cleanup workers from Ukraine exposed to ionizing gamma-ray radiation
[b]Sex- and age-matched CLL cases from the general population of Ukraine unexposed to ionizing radiation
[c]NaN = Not Available
[d]NA = Not Applicable

associated with poor prognosis in CLL patients [24, 25], we tested the trend of median survival of the 4 *POT1*-mutated UR-CLL cases. Results were not significantly different from the other UR-CLL cases, but a trend was observed indicating better prognosis of *POT1* mutation bearing-cases (median 5.3 years vs. 3.6 years, *POT1*-mutated vs. other UR-CLL cases, $p = 0.74$).

Discussion

This study was conducted to understand the effect of IR on CLL development and progression in a series of high-quality DNA specimens with corresponding radiation dosimetry and clinical information. Radiation exposure arose from a 'natural experiment' (i.e., an individual's exposure status was determined by outside forces but resembled random assignment). To our knowledge, this is the first study of genetic characteristics of CLL specimens in relation to individual radiation doses. Unfortunately, we could not perform this study on a larger sample set, and therefore the findings described here should be treated as a valuable case-series with unique preliminary and valuable data for guiding future research hypotheses.

Absence of statistically significant differences in frequencies of CNAs between UR-CLL, UN-CLL, and W-CLL indicated a similar genomic architecture in radiation-exposed compared with unexposed cases, and in Ukrainian and Western cases.

Sherborne et al. identified mutation signature significantly associated with high-dose (total dose of 30 Gy) IR in multiple IR-induced malignancies [19]. We used their non-negative matrix factorization technique to identify IR-associated mutation signatures above genetic background in UR-CLL. Specific pattern of preferred nucleotide substitutions, associated with IR exposure could not be resolved in mutations accumulated and identified in UR-CLL. This suggests that protracted exposure to low-dose radiation did not appear to induce widespread genomic changes via a specific mutational mechanism. However, our study might be underpowered to detect such a signature due to an insufficient number of mutations observed per case or the relatively low bone marrow doses estimated for UR-CLL

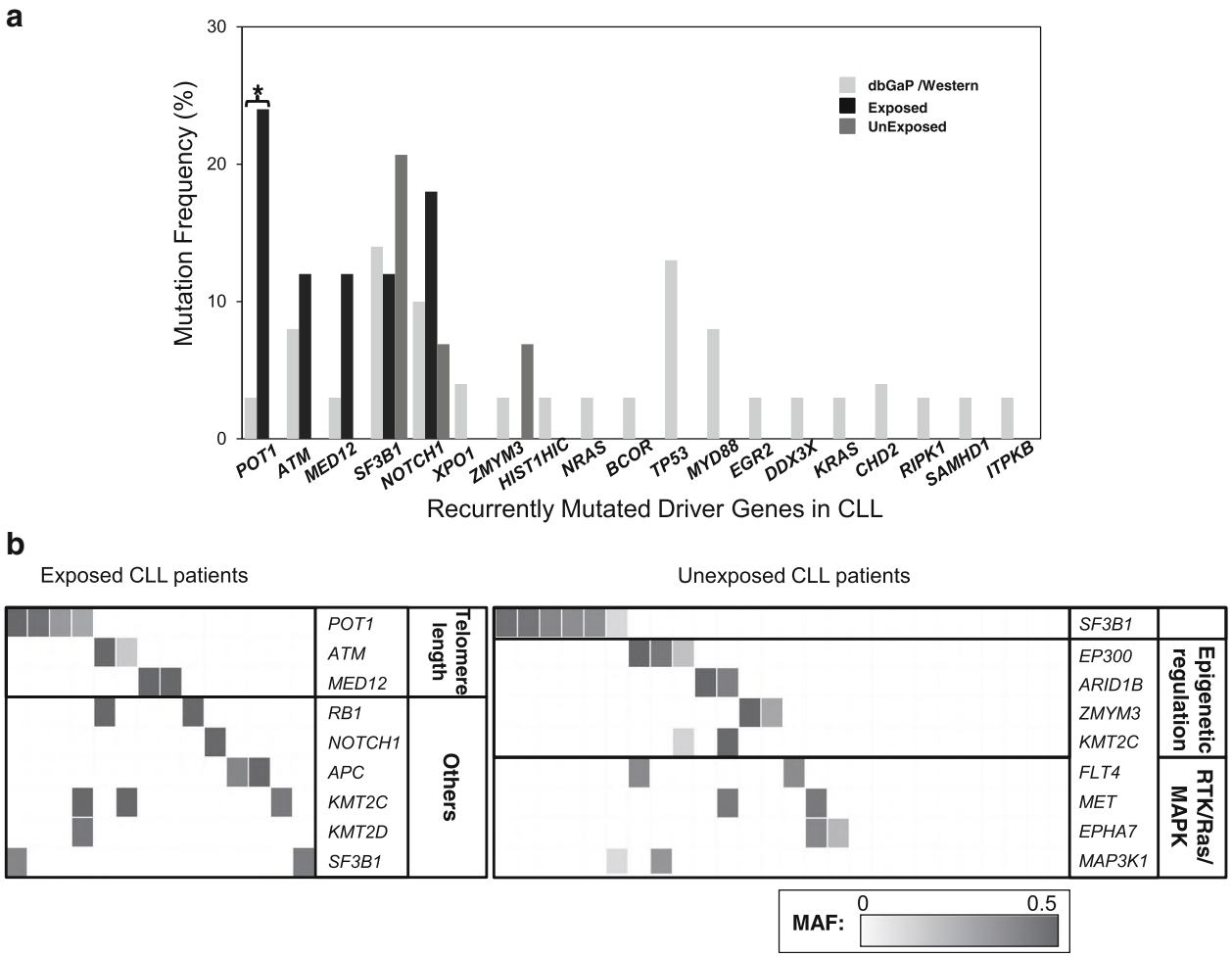

Fig. 1 Genomic landscape of CLL cases. (**a**) Prevalence of driver mutations, as defined in Landau et al. [23] in Western-CLL (dbGaP/Western; W-CLL cases from previous sequencing studies, light gray bars), Chornobyl cleanup workers with CLL (Exposed; UR-CLL, black bars) and unexposed Ukrainian CLL cases (UnExpsed; UN-CLL, gray bars). The asterisks identify significant comparisons ($p < 0.05$); (**b**) Tiling plot of predicted damaging mutations in exposed (UR-CLL) and unexposed (UN-CLL) Ukrainian patients. Horizontal rows depict mutations in a particular gene and functional category, and vertical columns represent individual patients (exposed and unexposed). Patients without mutations were excluded from the figure. Mutations are shaded according to their mutant allele fraction (MAF)

patients. Low bone marrow doses of UR-CLL might also explain the lack of expected genomic instability.

We identified enrichment of mutations in genes with roles in epigenetic regulation (*EP300*, *ARID1B*, *ZMYM3*, *KMT2C*) and the Ras/MAPK signaling pathway (*FLT4*, *MET*, *EPHA7*, *MAP3K1*), consistent with previous studies [23].

Although we did not identify a radiation-associated mutation signature in UR-CLL cases, our pathway analyses did reveal an enrichment of mutations in telomere-maintenance genes. *POT1*, *ATM*, and *RB1* all have reported roles in telomere maintenance [26]. The most frequently mutated gene in UR-CLL was *POT1* (*Protection of Telomeres 1*), and it was mutated at significantly higher frequency than in UN-CLL or W-CLL. *POT1* is one of six members of shelterin, a protein complex that binds telomeres. Additional shelterin complex proteins are encoded by *TERF1*, *TERF2*, *TINF2*, *TERF2IP*, and *ACD*. Three shelterin subunit proteins, including POT1, directly bind to the telomeric hexanucleotide repeats [27]. Previous studies have shown that localization of mutant *POT1* protein to the telomere causes dominant-negative telomere lengthening and telomere uncapping, leading to unprotected telomere ends and chromosomal fusions in CLL tumors [24]. Interestingly, all 4 *POT1* mutations detected in UR-CLL lie in OB-fold domains 1 & 2, which interacts with telomeric DNA and provides specific binding to various ligands [28]. These results suggest that we have identified functional *POT1* mutations likely to be involved in telomere uncapping and telomere lengthening. Similarly, recurrent *ATM* mutations that we identified were also localized in functional

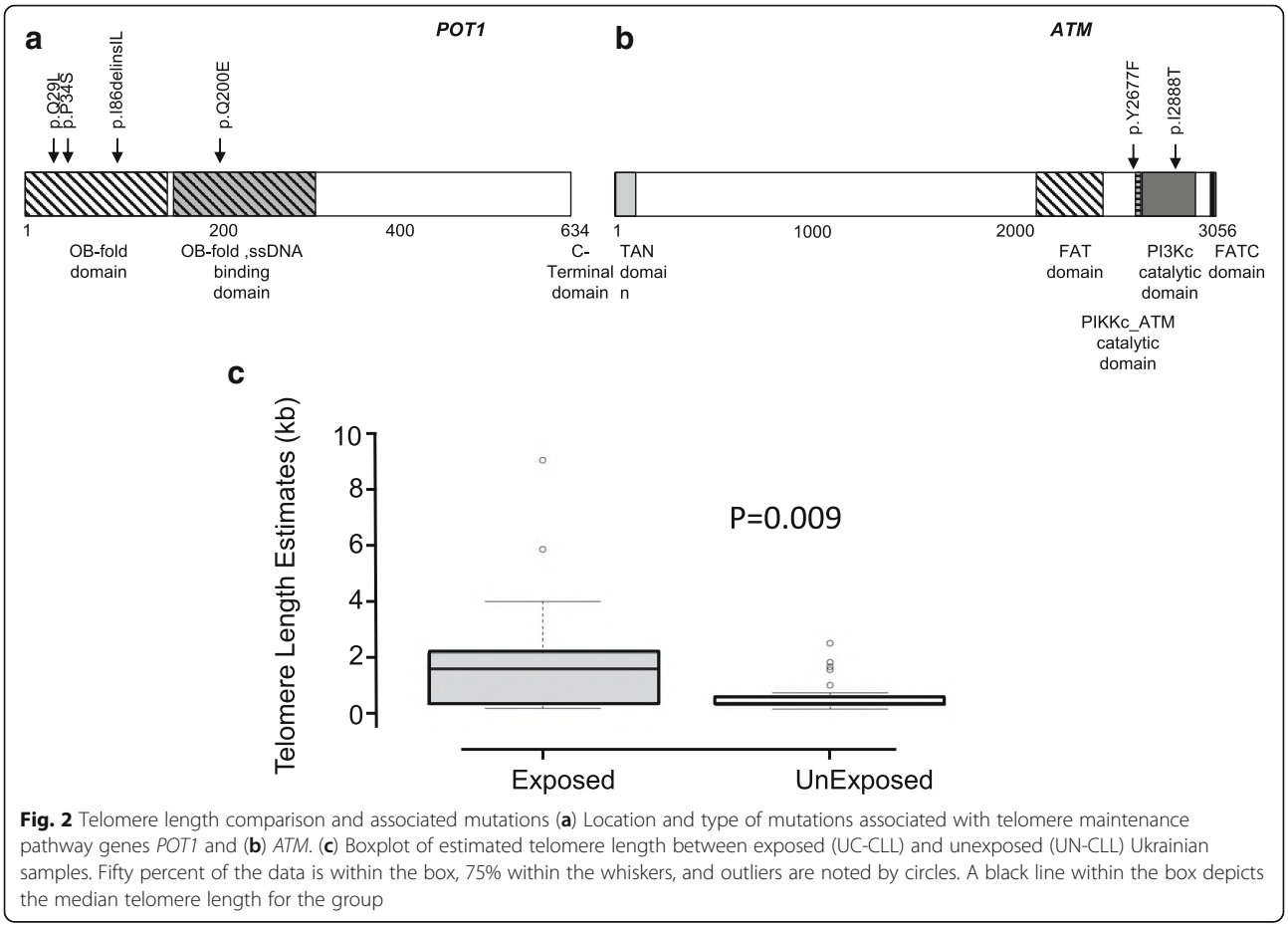

Fig. 2 Telomere length comparison and associated mutations (**a**) Location and type of mutations associated with telomere maintenance pathway genes *POT1* and (**b**) *ATM*. (**c**) Boxplot of estimated telomere length between exposed (UC-CLL) and unexposed (UN-CLL) Ukrainian samples. Fifty percent of the data is within the box, 75% within the whiskers, and outliers are noted by circles. A black line within the box depicts the median telomere length for the group

domains. Although no direct association of *MED12* has been identified with telomere biology, *MED12* mutations in association with *TERT* promoter mutations and increased telomere length have been reported in different tumors [29].

Previous studies suggest that radiation exposure is associated with telomere attrition [30], especially in males. However, studies of Chornobyl cleanup workers reported associations between longer telomere length and increased cancer diagnoses [31]. This is particularly compelling for CLL, as recent studies have established longer telomere length in healthy lymphocytes as a risk factor for future development of CLL [32, 33]. Our observation that radiation exposure was associated with longer telomere length in UR-CLL tumors suggests that pre-malignant B-cells in radiation-exposed men may be under strong selective pressure to circumvent growth arrest caused by telomere attrition. Somatic cells can undergo a host of different genetic and epigenetic mechanisms to lengthen telomeres, including reactivation of telomerase or alternative lengthening of telomeres (ALT). The observed frequency of *POT1* mutations in UR-CLL (25%) is much higher than in recent studies of radiation-unexposed CLL patients (3.5% to 9% [24]). Our observation that UR-CLL patients were likelier to harbor mutations in telomere-maintenance genes fits this proposed model.

Although survival of UR-CLL patients with *POT1* mutation was longer compared to other UR-CLL patients, this finding was based on a small number of cases and should be examined in future studies. Follow-up of all 79 CLL cases diagnosed in the Ukrainian-American Study of Leukemia and Related Disorders among Chornobyl Cleanup Workers from Ukraine indicated median overall survival of 4.8 years (range 0.5–19.5, 5-year survival rate of 46.2%) [8]. This is substantially lower than survival of U.S. CLL patients from the SEER database (5-year survival rate of 83.2%) [34].

Although the incidence of CLL is substantially higher in Ukraine than in Western countries, we observed a great deal of similarity between the somatic genomes of UN-CLL cases and W-CLL cases. Both groups had frequent mutations in *NOTCH1*, had similar CNA profiles, and were enriched for mutations in genes with roles in epigenetic regulation and the Ras/MAPK signaling pathway. These data suggest that there is a similar somatic genomic architecture in non-irradiated Ukrainian CLL patients and in Western CLL patients. Therefore, the

differences in incidence rates of CLL across these groups may be attributable to other factors, such as the frequency of heritable genetic variants or the prevalence of other environmental risk factors.

Conclusions

We conducted a comprehensive three-way comparison of UR-CLL, UN-CLL and W-CLL to understand the relationship of IR with CLL etiology. Ukrainian CLL patients with no history of radiation exposures had similar somatic genomic architecture to Western CLL patients. Our analysis of CLL patients exposed to IR due to clean up work after the Chornobyl accident suggests that dose to the bone marrow is correlated with an increase in burden of driver lesions in a dose-dependent manner. Further, longer telomere length in tumors and mutations in telomere-maintenance genes indicate a potential role for telomere biology in the genesis of radiation-associated CLL. No other mutations were found in genes clinically associated with chemorefractoriness or affecting survival. Future analyses of larger patient sets in radiation-associated cancer types can help bolster these findings. To our knowledge, this is the first study to perform an in-depth genomic characterization of CLL in Chornobyl cleanup workers, highlighting a potentially important role for telomere biology in leukemogenesis.

Endnotes

[1]The date of diagnosis for each individual is the first date recorded when the absolute number of lymphocytes in the peripheral blood exceeded 5000/μL.

[2]All cleanup workers registered in the State Chornobyl Registry were eligible for an annual health examination, which included a differential blood count and consultation with a physician. These examinations usually were conducted at a regional health facility.

Additional file

Additional file 1: Table S1. List of target genes sequenced by targeted deep sequencing. **Table S2.** Mutations in Exposed and Unexposed Cases. **Table S3.** Copy Number Aberrations (CNA) in Exposed and Unexposed Cases. (DOCX 311 kb)

Abbreviations

A-bomb: Atomic bomb; ALT: Alternative lengthening of telomeres; ANOVA: One-way analysis of variance; BWA: Burrows-Wheeler Aligner; CADD: Combined annotation dependent depletion; CLL: Chronic lymphocytic leukemia; CNA: Copy number abnormalities; ExAC: Exome aggregation consortium; GATK: Genome analysis toolkit; INDEL: Insertion and deletion; IR: Ionizing radiation; mTRF: Mean terminal restriction fragments; NMF: Non-negative matrix factorization; POT1: Protection of Telomeres 1; SNVs: Single nucleotide variants; TDS: Targeted deep sequencing; UN-CLL: Ukrainian non-irradiated patients with chronic lymphocytic leukemia; UR-CLL: Ukrainian Chornobyl Cleanup Workers with chronic lymphocytic leukemia; W- CLL: Western patients with chronic lymphocytic leukemia

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JO designed and performed research, analyzed data and wrote the paper. ADS, SG, MZ, HMH, ALS, JN, PMB, MH, MPL contributed to the analysis of data and preparation of the paper. SF, RR, NG, NB, VVC, DB participated in data collection, data analysis and preparation of the paper. KMW, JLW designed and performed research, analyzed data and wrote the paper. LBZ designed research, participated in data collection, performed data analysis and wrote the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The protocol for the study was approved by the institutional review boards of the University of California, San Francisco, School of Medicine (San Francisco, CA, USA) and NRCRM (Kyiv, Ukraine). All participants signed written consent forms.

Competing interests

The authors declare that they have no competing interests.

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Original Research Article

Clinical characteristics of chronic lymphocytic leukemia occurring in chornobyl cleanup workers

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Abstract

The recently demonstrated radiation-induction of chronic lymphocytic leukemia (CLL) raises the question as to whether the amount of radiation exposure influences any of the clinical characteristics of the disease. We evaluated the relationship between bone marrow radiation doses and clinical characteristics and survival of 79 CLL cases diagnosed during 1986–2006 in a cohort of 110 645 male workers who participated in the cleanup work of the Chornobyl nuclear accident in Ukraine in 1986. All diagnoses were confirmed by an independent International Hematology Panel. Patients were followed up to the date of death or end of follow-up on 31 October 2010. The median age at diagnosis was 57 years. Median bone marrow dose was 22.6 milligray (mGy) and was not associated with time between exposure and clinical diagnosis of CLL (latent period), age, peripheral blood lymphocyte count or clinical stage of disease in univariate and multivariate analyses. Latent period was significantly shorter among those older at first exposure, smokers and those with higher frequency of visits to the doctor prior to diagnosis. A significant increase in the risk of death with increasing radiation dose was observed ($p = 0.03$, hazard ratio = 2.38, 95% confidence interval: 1.11,5.08 comparing those with doses ≥22 mGy to doses <22 mGy). After adjustment for radiation dose, survival of CLL cases was significantly shorter among those with younger age at first exposure, higher peripheral blood lymphocyte count, more advanced clinical stage of disease and older age at diagnosis (all $p < 0.05$). This is the first study to examine association between bone marrow radiation doses from the Chornobyl accident and clinical manifestations of the CLL in Chornobyl cleanup workers. The current study provides new evidence on the association of radiation dose and younger age at first radiation exposure at Chornobyl with shorter survival after diagnosis. Future studies are necessary with more cases in order to improve the statistical power of these analyses and to determine their significance.

Keywords: **chronic lymphocytic leukemia; Chornobyl; Chernobyl; radiation; cleanup worker**

Introduction

Our recent case–control study covering 20 years of follow-up (1986–2006) of the cohort of 110 645 Chornobyl (Chernobyl) cleanup workers from Ukraine reported, for the first time in a large population, statistically significant evidence that chronic lymphocytic leukemia (CLL) may be induced from exposure to ionizing radiation [1]. A study of Chornobyl cleanup workers from Belarus, Russia and the Baltic countries, which used a study design similar to ours and an identical radiation dose estimation method, demonstrated a similar, although not statistically significant, radiation risk for CLL [2]. In contrast, the recent study of Russian cleanup workers based on the official reported

doses and Chernobyl Registry-based CLL diagnoses had negative findings [3].

It has been known, since the early 1950s from the Hiroshima and Nagasaki atomic bomb (A-bomb) survivor studies, that radiation exposure may induce most types of leukemia, but it generally has been accepted that radiation does not induce CLL [4]. However, the most recent follow-up of this population showed a significant linear dose-response for incident CLL [5]. Additional supportive evidence of a dose-related association between exposure to ionizing radiation and increased risk of incident CLL comes from some [6–8] but not all studies of occupationally exposed workers [9,10].

The emergence of CLL as a radiation-induced disease has raised questions as to whether these cases demonstrate any unusual clinical characteristics that might differ from idiopathic CLL. No unusual effects of ionizing radiation exposure on the clinical manifestations of leukemia have been observed in the A-bomb survivors [11]. That study, however, did not include any cases of CLL. We, therefore, thought important to determine if the radiation from the Chornobyl accident had influenced any of the measurable clinical manifestations of the leukemia or survival of the Chornobyl radiation-exposed cleanup workers with CLL.

Methods

Study population and case ascertainment

Study methods have been previously described [1,12,13]. Briefly, a cohort of 110 645 Ukrainian men who were 20–60 years of age during various cleanup activities in the 30-km zone around the 1986 nuclear reactor accident site at Chornobyl in Ukraine was formed from the list of workers registered in the State Chornobyl Registry. Cleanup workers resided in one of five oblasts (an oblast is an administrative area similar in size to a state or province), or in the city of Kyiv. Leukemia cases diagnosed in the cohort between the time of the reactor accident in 1986 and the year 2000 were identified by an intensive search of all regional hospitals, outpatient clinics, regional tumor clinics and other health agencies in the target areas [12]. Leukemia cases occurring between the years 2001 and 2006 were identified by linkage of the cohort file with the Ukrainian National Cancer Registry [1,14]. The medical records were available for 100% of the cases, and bone marrow aspiration smears, bone marrow biopsies and/or peripheral blood smears for approximately 70% of the cases. The diagnosis of CLL was based on the criteria established by the U.S. National Cancer Institute (NCI) Working Group [15], within the constraints of lymphocyte phenotype information from various outside laboratories which was available for 46% of the cases. All cases were reviewed by study hematologists (I.D., T.L. and V.B.), and later confirmed by an independent International Hematology Panel (see Acknowledgement).The current analysis is based on 79 of the 89 cases confirmed by the Panel for whom it was possible to reconstruct bone marrow radiation doses. One of the 79 cases included in the study was classified as small lymphocytic lymphoma (SLL).

Study protocol was approved by the institutional review boards of the NCI (Bethesda, MD, USA), the University of California, San Francisco (San Francisco, CA, USA) and the National Research Center for Radiation Medicine (Kyiv, Ukraine). All participants gave written informed consent.

Clinical characteristics

The following clinical characteristics were considered for a possible radiation effect: First: the latent period (interval of time in years between the date of first exposure and the date of diagnosis of CLL). The date of diagnosis for each individual is the first date recorded when the absolute number of lymphocytes in the peripheral blood exceeded 5000/μL. For the SLL case, the date of the histological diagnosis was used for the date of diagnosis. Second: age at the time of diagnosis. Third: stage of the disease, at the time of diagnosis of CLL, as measured by the Rai criteria [16]. Fourth: absolute number of peripheral blood lymphocytes at time of diagnosis, as calculated from the percent of lymphocytes in the differential blood count and the total leukocyte count. Fifth: survival, as measured in years following the date of diagnosis to the date of death or termination of the follow-up.

All cleanup workers registered in the State Chornobyl Registry were eligible for an annual health examination, which included a differential blood count and consultation with a physician. These examinations usually were conducted at a regional health facility.

Estimation of bone marrow radiation dose

Individual bone marrow doses were estimated from questionnaires and extensive environmental measurements taken immediately after the Chornobyl accident by means of the validated RADRUE method (Realistic Analytical Dose Reconstruction with Uncertainty Estimation) [17]. This method of dose estimation is dependent on such information as dates of work within the 30-km zone around Chornobyl, type of jobs performed, transportation routes and availability of official work history records. At no time, was dose information released to any clinician or case reviewer involved in the study.

Statistical methods

Regressions of estimated bone marrow doses with clinical variables were performed using un-lagged doses. Lag is a period of recent exposure assumed unrelated to disease.

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Analyses also were performed with 2-, 5-, 10- and 15-year lags and gave similar results (not shown).

Bone marrow radiation dose and latent period were not normally distributed. Therefore, all further univariate tests of these variables were done using a Wilcoxon–Mann–Whitney test. Mean age at first exposure had a normal distribution and all further univariate tests were done using one-way analysis of variance (ANOVA). Additional multivariate analyses of latent period were conducted using analysis of covariance (ANCOVA) and included categorical as well as continuous predictors.

Survival analyses were conducted using the Cox proportional hazards models [18]. The partial likelihood method was used to estimate the hazard of death from CLL and the 95% confidence interval around the estimate. For each case, we calculated the time interval from the diagnosis of CLL until death, the date last known to be alive, or the termination of follow-up on 31 October 2010, whichever occurred first.

All p values presented were two-sided. The best fitting models were chosen by using the likelihood ratio test and Akaike Information Criterion [19]. Independent predictors were retained in the model if they changed hazard ratio by more than 20% (survival analysis) or if they significantly improved the fit of the model at $p = 0.10$ (survival and ANCOVA analyses). All multivariate analyses excluded those with missing vital status (i), chemotherapy (ii) and demographic characteristics (iii), such as urban/rural status, alcohol consumption and smoking, reducing the final set for survival analysis to 73 CLL cases. All analyses were conducted using the SAS statistical software package [20].

Results

The estimated bone marrow radiation doses for the 79 CLL cases ranged from 0 to 1536.2 mGy with a median of

Table 1. Descriptive characteristics of CLL cases

Characteristics	All CLL cases (1986–2006) N = 79 (%)	Reduced set of CLL cases[a] N = 65 (%)	p-Value[d]
Bone marrow dose, median, mGy (range)	22.6 (0–1536.2)	23.5 (0–1536.2)	0.51
Age at first exposure, years, median (range)	45 (22–63)	46 (29–63)	0.50
22–34	11 (13.9)	8 (12.3)	
35–39	15 (19.0)	12 (18.5)	
40–44	14 (17.7)	9 (13.9)	
45–49	17 (21.5)	16 (24.6)	
50–54	11 (13.9)	10 (15.4)	
55–63	11 (13.9)	10 (15.4)	
Age at diagnosis, years, median (range)	57 (42–78)	57 (43–76)	0.94
42–44	6 (7.6)	5 (7.7)	
45–54	25 (31.7)	20 (30.8)	
55–64	35 (44.3)	28 (43.1)	
65–74	9 (11.4)	9 (13.9)	
75–78	4 (5.1)	3 (4.6)	
Latent period, years, median (range)	14 (1–20)	12 (1–20)	0.29
0–4	7 (8.9)	7 (10.8)	
5–9	18 (22.8)	17 (26.2)	
10–14	22 (27.9)	20 (30.8)	
15–20	32 (40.5)	21 (32.3)	
Urban/rural status[b]			0.72
Urban	62 (81.6)	52 (83.9)	
Rural	11 (14.5)	8 (12.9)	
Mixed	3 (4.0)	2 (3.2)	
Smoking[c]			0.80
Never/former	36 (48.0)	28 (45.9)	
10–20 cigarettes per day	24 (32.0)	20 (32.8)	
More than 20 cigarettes per day	15 (20.0)	13 (21.3)	
Alcohol consumption[b]			0.99
Never	20 (26.3)	16 (25.8)	
1–3 times per month	41 (54.0)	34 (54.8)	
Once per week–every day	15 (19.7)	12 (19.4)	

Abbreviations: mGy, milligray.
[a]Based on 65 cases with <2 years from start of chemotherapy to interview.
[b]Among 76 subjects with known information on urban/rural status and alcohol consumption.
[c]Among 75 subjects with known information on smoking.
[d]p-Value for heterogeneity from the Wilcoxon Rank Sum test or one-way analysis of variance (ANOVA) for continuous variables and Kruskal-Wallis test for multi-level variables.

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22.6 mGy (Table 1). The distribution was heavily skewed toward lower doses (Figure 1), with 56 (70.9%) of CLL cases having doses <100 mGy. Median age at first exposure was 45 years, and median age at diagnosis was 57 years. The majority of the cases (68.4%) were diagnosed more than 10 years after exposure in the Chornobyl zone (Table 1). Cases were predominately urban residents and reported relatively heavy smoking and alcohol consumption.

Previous analyses of this study population suggested possibly unreliable information for 14 of the 79 cases because interviews were conducted at the time when they were receiving or recovering from chemotherapy [1]. There were no appreciable differences in the distribution of disease characteristics in the two samples (all p-values > 0.2, Table 1) and all further analyses were conducted for all 79 cases.

In univariate analyses of 79 CLL cases (Table 2), median bone marrow radiation dose was not associated with Rai stage at diagnosis ($p = 0.25$) and peripheral blood lymphocyte count at the time of diagnosis ($p = 0.53$), although there was a monotonic trend to lower lymphocyte counts at higher doses. Latent period ($p = 0.82$), and the age at diagnosis ($p = 0.41$) also were not associated with median bone marrow radiation dose. However, latent period was significantly associated with the mean age at first exposure, with those older at exposure being diagnosed sooner ($p = 0.01$). The administration of chemotherapy was not significantly related to either the median bone marrow radiation dose ($p = 0.39$) or the mean age at first exposure ($p = 0.27$). Radiation dose was strongly associated with the average frequency of visits to the doctor prior to CLL diagnosis ($p < 0.01$); the higher the dose the more frequent the visits. Those with more than one visit every 2 years, had an almost three-fold higher median bone marrow dose, compared to those with no doctor visits, prior to diagnosis (median bone marrow doses of 56 and 18 mGy, respectively).

Multivariate ANCOVA analyses of latent period (Table 3) indicated that it was strongly associated with age at first exposure, smoking frequency and average frequency of visits to the doctor prior to diagnosis (all $p < 0.05$). As in the univariate analyses, latent period showed little association with bone marrow dose ($p = 0.84$). Overall, these four variables explained a third of the variation in time since exposure ($R^2 = 0.33$, not shown).

Median survival of 78 patients with complete follow-up information was 4.8 years (range 0.5–19.5). Figure 2 demonstrates Kaplan–Meier survival curves for five dose categories and number of subjects at risk. Those with the highest cumulative bone marrow doses (200–1536 mGy) had the shortest survival, although the differences in survival between various dose categories were not statistically significant (Log Rank $p = 0.22$). Use of the Akaike Information Criterion suggests that the dichotomous model is optimal among the three dose-response models considered (linear, dichotomous, 5-level categorical). Table 4 presents the results of Cox regression analyses and shows that survival of CLL cases was significantly related to bone marrow radiation dose ($p = 0.03$) with a hazard ratio (HR) of 2.38 comparing survival of those with doses above the median dose of 22 mGy to those with doses below. When the dose variable was split into five categories with approximately even number of cases in each, HRs for survival monotonically increased with increasing bone

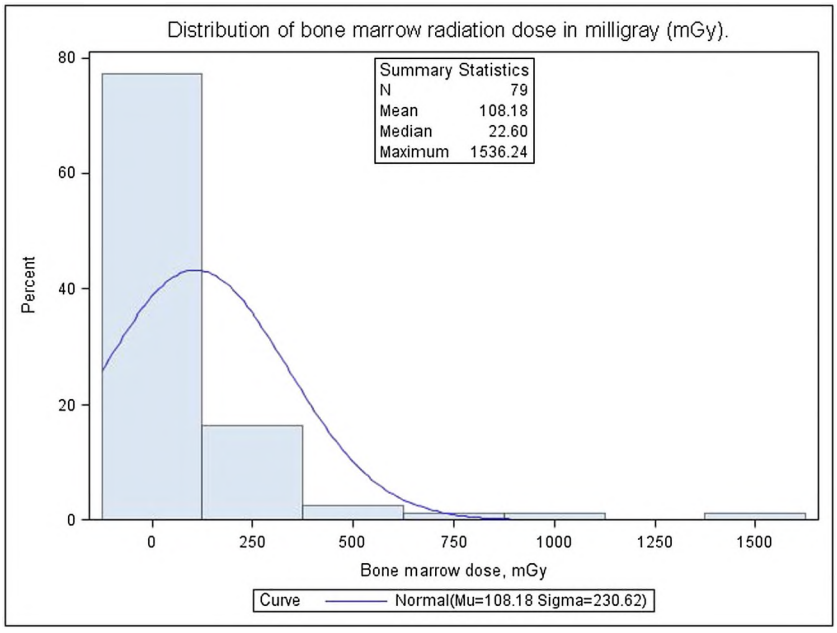

Figure 1. Distribution of bone marrow doses among CLL cases ($n = 79$). Kolmogorov–Smirnov Goodness-of-Fit test for normal distribution $p < 0.010$

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Table 2. Bone marrow dose and age at first exposure in the 30-km Chornobyl zone by categories of various characteristics

Characteristics	*N* cases = 79	Median bone marrow dose, mGy	DOF	*p*-Value[a]	Mean age at first exposure, years	*p*-Value[b]
Rai stage			4	0.25		0.15
0	4	12.8			40	
1	25	43.7			44	
2	33	15.8			46	
3	10	3.9			41	
4	7	22.6			51	
Absolute lymphocyte count at diagnosis, per mm^3 [c]			3	0.53		0.42
<10 000	18	49.9			44	
10 000–19 000	17	36.7			42	
20 000–39 000	21	19.8			46	
≥40 000	21	4.1			46	
Latent period, years			3	0.82		0.01
0–4	7	43			51	
5–9	18	22.7			47	
10–14	22	14.1			46	
15–20	32	37.4			41	
Age at diagnosis, years			4	0.41		<0.001
42–44	6	14.2			33	
45–54	25	38.2			39	
55–64	35	22.7			46	
65–74	9	21.9			56	
75–78	4	3.1			59	
Chemotherapy[d]			1	0.39		0.27
Yes	66	20.0			44	
No	11	33.6			47	
Average frequency of visits to the doctor prior to diagnosis			2	<0.01		0.05
0	22	18.0			49	
Once per 2 years	29	4.2			44	
More than once per 2 years	28	56.0			43	

Abbreviations: DOF, degrees of freedom; ANOVA, analysis of variance.
[a]*p*-Value for heterogeneity from the Wilcoxon Rank Sum test for chemotherapy and Kruskal-Wallis test for multi-level variables.
[b]*p*-Value for heterogeneity from the one-way ANOVA.
[c]Among 77 subjects with known information about lymphocyte count.
[d]Among 77 subjects with known information about chemotherapy.

Table 3. Analysis of factors associated with latent period [a]

Source	DOF	Type I SS[b]	Mean square	*F* value	*p*-Value[c]
Age at first exposure, years	1	231.46	231.46	13.52	<0.01
Smoking	2	172.08	86.04	5.02	<0.01
Average frequency of visits to the doctor, per 2 years	1	160.10	160.10	9.35	<0.01
Bone marrow dose, mGy	1	0.69	0.69	0.04	0.84
Source	**DOF**	**Type III SS[d]**	**Mean square**	***F* value**	**p-Value[e]**
Age at first exposure, years	1	135.86	135.86	7.93	<0.01
Smoking	2	126.85	63.43	3.70	0.03
Average frequency of visits to the doctor, per 2 years	1	158.40	158.40	9.25	<0.01
Bone marrow dose, mGy	1	0.69	0.69	0.04	0.84

Abbreviations: DOF, degrees of freedom; SS, sum of squares.
[a]For 74 CLL cases with available information on smoking.
[b]Indicates the reduction in the sequential error sum of squares with addition of each variable.
[c]*p*-Value from the analysis of covariance adjusted for all variables above the test variable.
[d]Indicates error sum of squares computed by comparing the full model to the model without the test variable.
[e]*p*-Value from the analysis of covariance adjusted for all other factors in the table.

marrow radiation dose, with HRs ranging from 1.79 for those with doses 2–19 mGy to 4.21 for those with doses 200–1536 mGy, compared to those with doses below 2 mGy (not shown). However, the test for linear trend

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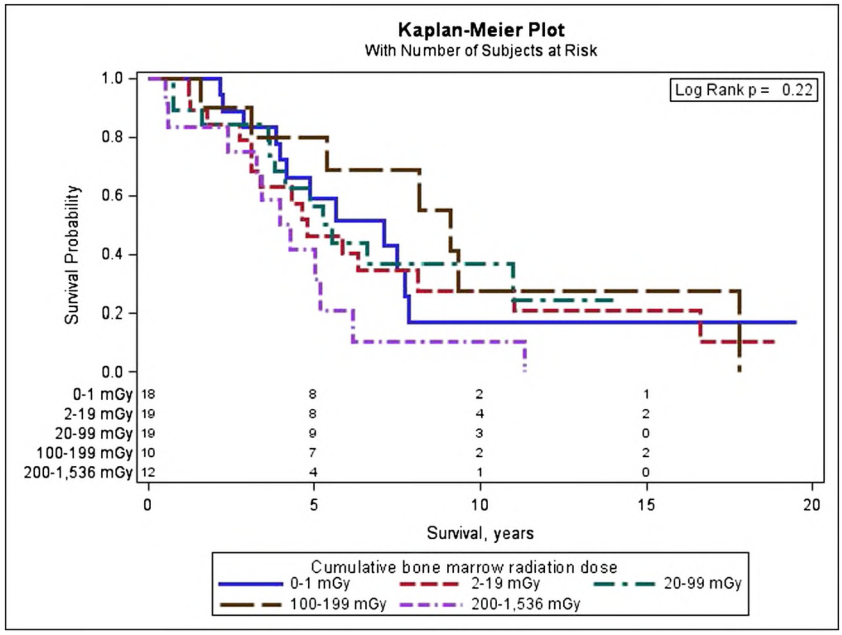

Figure 2. Kaplan–Meier plot for categories of bone marrow dose among CLL cases with survival information until 31 October 2010 ($n = 78$)

Table 4. Analysis of factors associated with survival of CLL cases [a, b]

Variable	Value	*N* cases = 73	Hazard ratio (95% CI)[c]	DOF	*p*-Value[d]
Bone marrow dose, mGy[e]	0–21	36	1	1	0.03
	22–1536	37	2.38 (1.11, 5.08)		
Age at diagnosis, years	Per 10 years increase		2.50 (1.09, 5.73)	1	0.03
Age at first exposure, years	Per 10 years increase		0.41 (0.19, 0.88)	1	0.02
Absolute lymphocyte count at diagnosis, per mm^3	1533–10 000	17	1	3	<0.01
	10 000–19 000	17	0.83 (0.27, 2.56)		
	20 000–39 000	19	1.79 (0.62, 5.18)		
	40 000–1 089 000	20	5.02 (1.69, 14.9)		
Rai stage	Stage 0–2	57	1	1	<0.01
	Stage 3–4	16	2.98 (1.32, 6.75)		
Chemotherapy	No	9	1	1	0.01
	Yes	64	13.5 (1.63, 112)		
Smoking	Never/former	34	1	2	0.06
	10–20 cigarettes per day	24	0.83 (0.39, 1.78)		
	More than 20 cigarettes per day	15	2.46 (1.01, 5.98)		
Alcohol consumption	Never	19	1	2	0.14
	1–3 times per month	39	1.16 (0.52, 2.62)		
	Once per week–every day	15	2.79 (0.88, 8.85)		
Urban/rural status	Urban	59	1	2	0.20
	Rural	11	0.43 (0.17, 1.12)		
	Mixed	3	1.25 (0.19, 8.38)		

Abbreviations: CI, confidence interval; DOF, degrees of freedom; mGy, milligray.
[a]For 73 CLL cases with known vital status and available information on chemotherapy, smoking and alcohol consumption and urban/rural status.
[b]Survival is defined as time from diagnosis to death or end of follow-up on 31 October 2010.
[c]Maximum likelihood confidence limits.
[d]*p*-Value from the likelihood ratio test comparing full model with all variables to the nested model without the variable of interest.
[e]Unlagged bone marrow doses; similar risks were estimated for doses lagged by 2, 5, 10 and 15 years.

was not statistically significant (p = 0.19, not shown). Other clinical characteristics associated with significantly poorer survival included later age at time of diagnosis, higher absolute lymphocyte count at time of diagnosis, Rai stage at time of diagnosis and the administration of chemotherapy (all $p < 0.05$, Table 4). Overall, 86% of

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the CLL patients had received chemotherapy by the end of follow-up on 31 October 2010. Survival was significantly shorter among those who were younger at first exposure ($p = 0.02$). Although not statistically significant, we observed that cleanup workers who were heavy smokers ($p = 0.06$) or alcohol drinkers ($p = 0.14$) had relatively poorer survival.

Discussion

This is the first study to examine association between bone marrow radiation doses from the Chornobyl accident and clinical manifestations of the CLL which had developed in the cleanup workers. Our previous study, based in a cohort of 110 645 male cleanup workers of the Chornobyl accident in Ukraine in 1986, showed a significant dose-related increase in the risk of CLL in analyses comparing CLL cases and controls and estimated that about 20% of CLL cases could be attributed to radiation exposure from cleanup work [1]. In the current study, we analyzed 79 cases of CLL which have been confirmed by the International Hematology Panel. We observed that higher radiation doses and younger age at first exposure to radiation during Chornobyl cleanup work were associated with significantly shorter survival. Latent period was not associated with bone marrow radiation dose, stage of disease, chemotherapy treatment or any other clinical characteristics. However, we estimated that older age at first exposure, smoking and higher frequency of visits to the doctor were significantly associated with a shorter latent period.

The issue of radiation-related risks of CLL has been controversial for many years [21]. While earlier studies of A-bomb survivors from Japan reported no increase in radiation risks [22], a recent report based on12 cases of CLL identified in a cohort of about 113 000 survivors from 1950 to 2001 (3% of 371 cases of all leukemia) and using a simple age and gender baseline model, reported a significant linear radiation dose-response [5]. It now seems clear that the major reason for the previous negative findings with regards to radiogenicity of CLL in the A-bomb survivors was, most likely, because of very low incidence of CLL in the Japanese population (2–3% of all cases of leukemia [23,24]) compared to Caucasian populations (about 40% based on registry data [25]).

The evidence on radiation-related risks of CLL from incidence studies of Caucasian populations exposed to low doses of ionizing radiation continues to be mixed, with some showing no increase in risks [3,9,10,26] while others reporting a dose-related association [6–8,27]. Finch and Linet [28] have noted that over a quarter of all CLL cases may be asymptomatic for many years, and that survival is significantly longer compared to other types of leukemia. In addition, several recent publications have suggested that mortality studies based on death certificates are not very reliable [29,30], while other studies suggested that they could underestimate CLL occurrence by as much as 38% [31]. Thus, mortality data would underestimate, possibly substantially, the occurrence of CLL. Other problems with the detection of the possible radiation induction of CLL include short follow-up and small sample size [32]. For example, the first analysis of incidence data from the Techa River cohort reported a negative radiation risk estimate for CLL based on 1953–2005 follow-up with 22 CLL cases [26], while the second analysis based on 1953–2007 follow-up with 27 CLL cases showed non-significantly increased risks (ERR/Gy = 0.01, 95% CI: <0, 1.2) [27]. We note that in the past, serious concerns have been raised about studies of Russian cleanup workers based on official doses and unverified diagnoses from the Chernobyl Registry; thus, negative findings from this study should be treated with caution [33].

We were particularly interested in examining the effects of radiation exposures and the age at time of first exposure on the latent period on the basis of two previous reports of apparent alterations in the clinical course of leukemia because of induction by radiation or a chemical [34,35]. An early report concerning children with acute leukemia from the study of A-bomb survivors in Hiroshima and Nagasaki indicated that younger age at time of exposure was associated with a shorter latent period prior to the appearance of clinical disease [34]. The median age at CLL diagnosis in our study was 57 years compared to the median age at diagnosis in the US of 72 years [36]. A recent study of 195 adult veterans who were exposed to Agent Orange and developed CLL showed no differences between the exposed and non-exposed for Rai staging, lymphocyte doubling time, cytogenetic changes or survival [35]. However, the Agent Orange exposed veterans were both significantly younger at time of diagnosis and the latent period was significantly shorter than it was for the non-exposed veterans. In our study, the median latent period was 14 years, and both univariate and multivariate analyses showed no association of latent period with bone marrow radiation doses but a significant association with age at first exposure.

Our study provides important insights into the relationship between radiation exposure and survival of CLL cases from among radiation-exposed Chornobyl cleanup workers. Earlier studies of the cleanup workers reported that exposed to radiation had a more aggressive clinical course compared to those non- or little exposed [37]. The authors speculated that aggressive behavior could be explained by alterations in immunoglobulin variable heavy chain gene configuration [38]. In contrast to these studies, we had individual bone marrow doses for all CLL cases. Our analyses showed a significant dose-related increase in the hazard of dying. Whether this impaired survival is

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related to radiation exposure, per se, or other radiation comorbidities or some other factors is not clear at this time. Higher median bone marrow doses were also associated with higher average frequency of visits to the doctor prior to diagnosis (Table 2). The overall infrequency of visits prior to the diagnosis of CLL (27.8% never visited a doctor prior to diagnosis and 36.7% visited no more than once per 2 years) may explain why the disease was quite advanced at the time of diagnosis of CLL for many of the workers (50% being diagnosed at stage two or higher, Table 4). This argues against any possible screening bias. The majority of CLL cases received chemotherapy, and many were started on chemotherapy within a few days of disease diagnosis.

Our results need to be considered in light of several strengths and limitations. The results of the physical examination and clinical laboratory observations were recorded for each case at the time the diagnosis of leukemia was established [12] and greatly enhanced the quality of the incidence study. It is possible that some leukemia cases were missed, particularly those with shorter latent periods. However, all cleanup workers were registered in the Chornobyl State Registry and received pension benefits, so it is unlikely that we missed a large number of cases. Certain environmental factors and even local or national personal customs could have confounded our results. For example, a number of studies of farming populations now strongly suggest that pesticides and/or herbicides play a likely role in the etiology of CLL [39,40]. However, in our study, occupational exposures to pesticides, solvents and benzene were not independent risk factors of CLL [13,41].

Conclusion

Analysis of 79 cases of CLL cases identified over 20 years of follow-up of a large cohort of Chornobyl cleanup workers from Ukraine showed that latent period was not associated with bone marrow radiation doses or any clinical characteristics but was significantly shorter among those older at first exposure, smokers and those with higher frequency of visits to the doctor prior to diagnosis. Higher bone marrow radiation doses and younger age as well as more advance disease stage at diagnosis were significantly associated with shorter survival. An increase in the risk of death with increasing bone marrow radiation dose requires further investigation to exclude effects of chance and unmeasured risk factors. Future studies are necessary with more cases in order to improve the statistical power of these analyses and to determine their significance.

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Conflict of interest

The authors have no competing interest.

Author contributions

S.C.F., R.F.R. and L.B.Z. contributed to the design of this clinical study, data acquisition, interpretation of results and preparation of the manuscript. I.D., N.G., N. B., T.L., V.B., A.R., V.C. and D.B. contributed to data acquisition and interpretation of results. A.B., M.H. and M.P.L. contributed to data acquisition, interpretation of the results and preparation of the manuscript. L.B.Z. analyzed the data.

Declarations

All authors have no relevant conflicts of interest.

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8. УЗАГАЛЬНЕННЯ ДОСЛІДЖЕНЬ ОНКОЛОГІЧНИХ ЕФЕКТІВ СЕРЕД УЧАСНИКІВ ЛНА В УКРАЇНІ: ВІД ЕПІДЕМІОЛОГІЇ ДО МОЛЕКУЛЯРНОЇ КІЛЬКІСНОЇ ОЦІНКИ

Підсумовуючи результати епідеміологічних досліджень стохастичних ефектів опромінення внаслідок аварії на Чорнобильській АЕС, треба підкреслити, що поряд із серією аналітичних досліджень, проведених в Україні, в яких отримано оцінки дозо залежних ризиків виникнення лейкемії та раку щитоподібної залози, в країні продовжуються широкомасштабні описові дослідження, враховуючи їхню відносну дешевизну і швидкість отримання необхідних оцінок.

Такі дослідження дозволяють проводити моніторинг загальних тенденцій захворюваності на злоякісні новоутворення і визначати напрями для більш поглиблених аналітичних досліджень, а також для молекулярних досліджень, які генерують і вивчають моделі патогенезу, чутливості і результат захворювань, ризики яких вивчаються в аналітичних епідеміологічних дослідженнях. Проведені дослідження демонструють можливість зрозуміти природу ефектів, викликаних радіацією, після впливу низьких доз. Нестабільність геному, включаючи підвищений вміст мікроядер, експресія гамма-H2AX, мінливість довжини теломер та зміни експресії генів можуть слугувати маркерами впливу низьких доз на здоров’я.

Оскільки ризик раку в досліджуваних когортах не був реалізований повністю, моніторинг та реєстри для його підтримки все ще залишаються актуальним завданням медичного спостереження

cancers

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Article

Cancers after Chornobyl: From Epidemiology to Molecular Quantification

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Abstract: An overview and new data are presented from cancer studies of the most exposed groups of the population after the Chornobyl accident, performed at the National Research Center for Radiation Medicine (NRCRM). Incidence rates of solid cancers were analyzed for the 1990–2016 period in cleanup workers, evacuees, and the general population from the contaminated areas. In male cleanup workers, the significant increase in rates was demonstrated for cancers in total, leukemia, lymphoma, and thyroid cancer, as well as breast cancer rates were increased in females. Significantly elevated thyroid cancer incidence was identified in the male cleanup workers cohort (150,813) in 1986–2012 with an overall standardized incidence ratio (SIR) of 3.35 (95% CI: 2.91–3.80). A slight decrease in incidence rates was registered starting at 25 years after exposure. In total, 32 of 57 deaths in a group of cleanup workers with confirmed acute radiation syndrome (ARS) or not confirmed ARS (ARS NC) were due to blood malignancies or cancer. Molecular studies in cohort members included gene expression and polymorphism, FISH, relative telomere length, immunophenotype, micronuclei test, histone H2AX, and TORCH infections. Analysis of chronic lymphocytic leukemia (CLL) cases from the cohort showed more frequent mutations in telomere maintenance pathway genes as compared with unexposed CLL patients.

Keywords: Chornobyl (Chernobyl); cleanup workers; leukemia; thyroid cancer; breast cancer; telomere length

1. Introduction

Exposure to ionizing radiation is associated with increased risk of cancer—primarily leukemia, thyroid, and breast cancer. The first reports on the effects of radiation exposure were published for the Japanese A-bomb survivors [1,2].

Later analysis showed an increased solid cancer incidence among the Life Span Study (LSS) atomic bomb survivors in Hiroshima and Nagasaki, using the updated case numbers and dosimetry in a cohort of 105,444 subjects. For females, the dose response was consistent with linearity, with an estimated excess relative risk (ERR) of 0.64 per Gy (95% CI: 0.52 to 0.77); for males, an ERR of 0.20 (95% CI: 0.12 to 0.28) at 1 Gy was demonstrated [3].

The leukemia results indicated that there was a nonlinear dose response for leukemias other than chronic lymphocytic leukemia or adult T-cell leukemia, which varied markedly with time and age at exposure. Although the leukemia excess risks generally declined with attained age or time since exposure, there was evidence that the radiation-associated excess leukemia risks, especially for acute myeloid leukemia, had persisted throughout the follow-up period out to 55 years after the bombings [4]. Chronic lymphocytic leukemia (CLL) risks were not analyzed as such pathology is absent in Japan and it has not occurred among radiation-exposed.

These effects were then confirmed by the numerous studies of populations exposed to medical or occupational radiation [5–7]. A study of associations between ionizing radiation and site-specific solid cancer mortality was performed among 308,297 nuclear workers employed in France, the United Kingdom, and the United States. The risks were shown for non-CLL leukaemia with an ERR of 2.96 per Gy, (90% CI = 1.17; 5.21), and between cumulative dose and mortality from solid cancers, with an ERR of 0.47 per Gy, (90% CI = 0.18; 0.79) Using a maximum-likelihood method, an attempt was made with the same cohort to quantify associations between radiation dose- and site-specific cancer [8,9]. Positive point estimates were obtained for lung, colon, and prostate cancers. Most of these estimated coefficients exhibited substantial imprecision.

Further evidence is needed regarding associations between cancer and low-dose radiation, and Chornobyl data could provide it.

Chornobyl findings were analyzed in the 2008 report of United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) [10]. Among cancers, only an increase of thyroid cancer rates was confirmed in those exposed at childhood. However, results of only a few cancer studies were available and analyzed at that time.

Studies of the general population exposed to 131I after the Chornobyl nuclear accident have demonstrated significant excess of thyroid cancers after exposure in childhood, which was substantially greater than originally expected [11]. Data on those exposed in adulthood are more controversial. Chornobyl cleanup workers likely experienced an increased risk of leukemia, already known to be a radiogenic cancer. Other possible health effects, which were not expected, include a possible increased risk for chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL), multiple myeloma, and thyroid cancer after adulthood exposure [11]. There are indications of the excess of radiogenic breast cancer that need further research. However, it is still not possible to separate radiogenic cancers from spontaneous cancers using the specific markers and epidemiology data could be questioned, as that led to the opinion of overestimation of Chornobyl effects on health [12]. The aim of the paper is to analyze the results of the national and international studies conducted at the National Research Center for Radiation Medicine (NRCRM) on health effects following the Chornobyl accident in Ukraine.

2. Study Subjects and Methods

A retrospective cancer incidence study was performed in cohorts of cleanup workers, evacuees from the 30 km exclusion zone, and different groups of the exposed population using the data of the Chornobyl State Registry of Ukraine (SRU). Their health status is being monitored in the local hospitals according to the national follow-up program [13]. As of 30 June 2015, a total of 318,988 cleanup workers were registered in the registry. In total, 196,423 of them were males involved in cleanup in 1986–1987 and 11,300 were females.

The data from the SRU were used to investigate the cancer incidence among the Chornobyl accident cleanup workers of 1986–1987 and among evacuees. The personified data of SRU on cancer patients were compared with the database of the National Cancer Registry of Ukraine (NCRU), providing the possibility to exclude all cases with incomplete verification of diagnosis and doubled data. After this procedure, all duplicates and cases without validated diagnosis were eliminated.

Notification of cancer cases has been mandatory in Ukraine since 1953, with the NCRU established in 1996. Cancer registration procedures at the NCRU are in accordance with international standards and recommendations. The proportion of microscopically verified cases increased from 73.6% in 2002 to 82.3% in 2012, with death-certificate-only proportions stable at around 0.1% and unknown stage recorded in 9.6% of male and 7.5% of female solid tumors. Timeliness was considered acceptable, with reporting >99% complete within a turn-around time of 15 months [14].

Linkage of SRU data with the NCRUdatabase made it possible to monitor incidence of malignant tumors of different sites in cleanup worker cohorts with an acceptable degree of confidence, and to formulate the hypotheses to test them in analytical studies.

At the territories contaminated with radionuclides after Chornobyl, collection of information on all cancer cases was performed in the Luginy, Narodichy, and Ovruch districts of the Zhitomir region, and the Borodyanka, Ivankov, and Polesskoye districts of the Kyiv region. For the data collection all relevant medical documents (including emergency notifications of new cancer cases as well as death certificates) were obtained from all medical institutions where these patients were diagnosed and treated.

Age specific and age standardized incidence rates were calculated for the period 1990–2016 and compared with respective data on Ukraine as a whole and also on the Zhitomir and Kyiv oblasts as those include the most contaminated territories. Age distribution of the world standard population was used as a standard.

One of the priority groups under the NRCRM follow-up included 190 from 237 cleanup workers who were citizens of Ukraine diagnosed with acute radiation syndrome (ARS). This group consisted of 91 confirmed ARS survivors and 99 patients who had no all symptoms of ARS according to current classification (ARS non-confirmed—NC) [15]. Doses of ARS patients, which were determined by biodosimetry methods after the accident, ranged from 0.1 to 7.1 Gy in ARS survivors and 0.1–1.0 Gy in ARS NC group [16].

In parallel to epidemiological studies a set of molecular investigations was performed among the Cohorts members. A study was performed on 235 male Chornobyl accident cleanup workers exposed in 1986–1987 (doses of external exposure: (M ± SD: 419.48 ± 654.60; range 0.10–3500 mSv)); mean age 58.34 ± 6.57 years. A control group included 45 nonexposed subjects (mean age: 50.60 ± 5.37 (M ± SD)). Gene expression was performed by RT-PCR on 7900 HT Analyzer using TLDA for *BCL2*, *CDKN2A*, *CLSTN2*, *GSTM1*, *IFNG*, *IL1B*, *MCF2L*, *SERPINB9*, *STAT3*, *TERF1*, *TERF2*, *TERT*, *TNF*, *TP53*, and *CCND1* genes. Relative telomere length (RTL) was analyzed by flow-FISH; immune cell subset expression, γ-H2AX; and CyclinD1, was measured by flow cytometry.

3. Results

Epidemiological studies on the health effects of the Chornobyl accident were initiated in collaboration with the international scientific community and were concentrated firstly on leukemia and thyroid cancer risks, accounting for their widely recognized link to ionizing radiation exposure.

Cancer effects in the general population were studied in inhabitants of radioactively contaminated areas of the Zhytomyr and Kyiv regions of Ukraine. In 1986, the cohort included 360,700 people exposed to radiation. In 2016, data were available on 170,600 individuals. The mean effective dose of external exposure was 22.4 mSv and thyroid dose was from 187 to 221 mGy. The number of cancers registered in the National Cancer Registry of Ukraine included 26,979 cases. We have not revealed an excess of solid cancers in total for all the period. Increased rates were registered for thyroid cancer. The expected number of thyroid cancer cases in a cohort for 1990–2016 period was 347.5, the observed number was 450 cases (SIR 129.5; 95% CI 117.5–141.5).

A cohort of evacuees from Prypiat, Chornobyl towns, and the 30 km exclusion zone were studied for the 1990–2016 period, which included 50,700 subjects in 1990 and 67,200 subjects in 2016, mainly due to continuation of relocation from areas adjacent to the 30 km zone. Doses of external exposure varied from 10 to 30 mSv, thyroid doses were in the range of 184.4–857.5 mGy. The number of registered solid cancer cases was 4,116, which was lower than expected according to the national standard. The number of observed thyroid cancer cases was 346 compared with 85.7 expected (SIR 403.7; 95% CI 361.2–446.3). Workers from Ukraine who participated in emergency response and cleanup were exposed to the highest doses [17]. As a result, they were expected to be the most affected population group in terms of radiation-induced cancers, and possibly noncancer diseases including cardiovascular ones.

Epidemiology studies in cleanup workers of 1986–1987 have shown an increased incidence of some cancer types diagnosed in 1994–2016. The follow-up continues. Among nosology forms, the most notable are leukemia, thyroid cancer (both genders), and breast cancer in female cleanup workers. A

total cancer incidence exceeded national levels during the postaccident period up to 2005. Starting from the 2006 the incidence rates differ from the national standards insignificantly (Table 1).

Table 1. Cancer standardized incidence ratios, SIRs, (95% CI), in Ukrainian Chornobyl cleanup workers (1986–1987, both genders) by follow-up period and cancer site.

Cancer Site		Period of Follow-Up			
	ICD–10	1994–1999	2000–2005	2006–2010	2011–2016
All cancers	C00–C96	138.3 (132.5–144.0)	107.1 (103.7–110.4)	103.3 (99.9–106.7)	102.6 (99.2–106.0)
Leukemia and lymphoma	C81–C96	232.6 (200.9–264.3)	201.8 (180.0–223.7)	123.9 (105.4–142.4)	140.8 (121.2–160.6)
Thyroid cancer	C73	554.9 (440.9–668.9)	666.7 (569.8–763.5)	322.2 (250.2–394.1)	250.3 (192.9–307.8)
Breast cancer	C50	185.2 (143.3–227.1)	176.1 (146.9–205.3)	140.3 (113.0–167.7)	130.4 (103.0–157.8)

Cancers and Leukemia in ARS Survivors

The NRCRM follow-up of those most exposed included a total of 190 subjects diagnosed with the acute radiation syndrome in 1986. From them, 91 diagnoses were confirmed during the re-evaluation three years later (ARS 1–3) and 99 were not confirmed (ARS NC). During the follow-up 57 patients had died in total, including 32 deaths that were caused by solid cancers or blood malignancies.

The first case of solid cancer was diagnosed 6 years after exposure in an ARS NC survivor. It is necessary to note that all following cases of solid tumors either developed without any clinical symptoms and were revealed by chance during routine examination or, following minimum nonspecific complaints (so called "syndrome of minor signs"), were revealed due to physicians' oncological experience. Over 33 years of follow-up, solid cancers developed in 12 ARS1-3 survivors and 12 patients of ARS-NC group. In the first group three cases of basal cell carcinoma (D04.4, D04.7), two prostate cancers (C61) (in one patient prostate cancer had combined with basal cell carcinoma), two thyroid cancers (C73), one case of urinary bladder (C67.8), one case of colon cancer (C18.7), one case of liver cancer (C22.0), one case of maxillary sinus cancer (C31.0), one tumor of the right cerebellopontine angle (C71.6), and one mandible neuroma with malignant transformation (C72.5) were detected. Four patients of ARS-NC were diagnosed with gastric cancer (C16.9), three colon cancers (C18.9), one case of kidney (C64), one case of prostate (C61), one case of lung (C34.2), and one case of throat (C32.8) cancers. Neoplasms caused the death of four ARS survivors and nine patients with ARS-NC. For both groups the time from the initial diagnosis of cancer and the onset of death was 1.3 ± 1.3 years, the age at a time of death 63.6 ± 13.2 years.

Leukemia and oncohematological disorders were diagnosed in eight survivors (six ARS and two ARS-NC). During the postaccidental period amongst ARS1-3 survivors, three cases of myelodysplastic syndrome (D46.1, D46.4, D46.9), one case of acute myelomonoblastic leukemia (C92.5), one case of chronic myeloid leukemia (C92.1), and one case of non-Hodgkin B-cell lymphoma (C83.8) were revealed. All patients died, but in case of non-Hodgkin lymphoma myocardial infarction was the reason of lethal outcome. In two ARS-NC patients hypoplasia of hematopoiesis (C96.9) and polycythemia vera (D45) developed that brought them to death. The patient with osteomyelofibrosis that transformed into acute myeloid leukemia (C92.0) is still alive. The difference between numbers of blood disorders in ARS survivors group (6.6%), and ARS NC (2.0%) was insignificant ($p > 0.05$).

The mean survival period from diagnosis to death was 2.0 ± 2.1 years in both ARS survivors and ARS-NC patients. The mean age of death from oncohematological disorders was 57.9 ± 6.9 years. Analysis showed that 45% of ARS1-3 and ARS-NC patients died at the age of less than 62.3 years, which, according to the WHO data, was the average life expectancy of males in Ukraine.

4. Discussion

To quantify the risks of radiogenic cancers caused by Chornobyl exposure and to find out whether it differs from the estimates received for the Japanese A-bomb survivors, the following analytical studies were initiated: A case-control study on leukemia and a case-control study on thyroid cancer in cleanup workers in Ukraine. To reveal missing leukemia cases, a special registry was created containing 41,000 patients of the same age, gender, and inhabitance areas with 99 hematological disorders that might resemble leukemia. All the diagnoses were re-evaluated by the national review group and sent for international pathology expertise.

It has been widely recognized since early 1950's Japanese studies that ionizing radiation may induce most types of leukemia, excluding chronic lymphocytic leukemia (CLL) [1,10]. A case-control study of Chornobyl cleanup workers in Belarus, Russia, and the Baltic countries demonstrated an elevated radiation-associated risk for CLL, though not statistically significant [18].

Moreover, the most recent atomic bomb survivor leukemia incidence study, showed a statistically significant linear dose-response for CLL [4]. Dose-related association between exposure to ionizing radiation and the increased incidence of CLL was also demonstrated in studies of occupationally exposed workers [19–21].

In Ukraine, a nested case-control study in a cohort of 110,645 male cleanup workers was performed together by the NRCRM and U.S. National Cancer Institute. Case identification and validation was performed by the international pathology review. Doses for cases and controls were reconstructed by a new RADRUE method [22,23]. For first 15 years, ERR/Gy value was 3.44 (95% CI 0.47; 9.78; $p < 0.01$) with surprisingly equal value for chronic lymphocytic leukemia and leukemia excluding CLL [24]. Further analysis for a 20 year period was based on an extended number of cases (160, among them 89 CLL). A significant linear dose response for 137 leukemia cases with reconstructed doses was identified, ERR/Gy = 1.26 (95% CI: 0.03–3.58). A detailed analysis has shown difficulties in a questionnaire-based dose reconstruction by RADRUE in 20 participants interviewed in a period less than 2 years after chemotherapy (ERR/Gy = −0.47 (95% CI: <−0.47 to 1.02)), presumably due to cognitive problems. For the remaining 117 cases, the ERR value was 2.38 (95% CI: 0.49–5.87), and a clearly demonstrated dose dependent excessive risk was demonstrated for either leukemia as a whole or leukemia subtypes separately. For CLL, the ERR/Gy was 2.58 (95% CI: 0.02–8.43), and for non-CLL, ERR/Gy was 2.21 (95% CI: 0.05–7.61). In total, 16% of leukemia cases (18% of CLL, 15% of non-CLL) were attributed to radiation exposure [25]. In a study of factors other than radiation after adjusting for radiation exposure, we identified a two-fold elevated risk for non-CLL leukemia for occupational exposure to petroleum, OR = 2.28 (95% CI: 1.13–6.79), mostly due to particularly high risk for myeloid leukemia. No associations with risk factors other than radiation were found for chronic lymphocytic leukemia [26].

In addition to CLL risk estimates, it was defined that older age at first exposure, smoking, and higher frequency of visits to the doctor were significantly associated with a shorter latent period. At the same time, the association of radiation dose and younger age at first radiation exposure at Chornobyl with shorter survival after diagnosis was shown, though not statistically significant [27].

Our present data on leukemia and lymphoma provide support to the mentioned studies as well as INWORKS analysis in radiation workers [9], and extend the elevated risks period up to 30 years after exposure. These results are in line with Japanese hibakusha data [1,2].

Thyroid cancer, along with leukemia, is the earliest manifestation of radiation exposure. The follow-up on the thyroid cancer frequency in a cohort of 150,813 male Chornobyl cleanup workers was launched in 1986 and originally continued through 2010 There were 196 followed-up incident thyroid cancer cases in the study cohort, with an overall SIR of 3.50 (95% CI: 3.04–4.03). A significantly elevated SIR estimate of 3.86 (95% CI: 3.26–4.57) was calculated for the cleanup workers who had their first cleanup mission in the Chornobyl zone in 1986 [28].

Continuation of the follow-up through 2012 [did not substantially change the values (Table 2). There were 216 incident thyroid cancer cases in the study cohort with an overall SIR of 3.35 (95% CI:

2.91–3.80). Elevated thyroid cancer incidence was detected in male cleanup workers who participated in cleanup activities during the entire period of cleanups (1986–1990), although it was statistically significant only among those who participated the activities held in 1986–1987, most possibly due to the difference in the dose (Table 2) [29].

Table 2. Number of thyroid cancer cases, person-years of observation, and SIR in the cohort of male Ukrainian cleanup workers (150,813) by year of first mission in the Chornobyl zone [29].

Year of First Mission	Number of Cleanup Workers	Person-Years	Thyroid Cancer Cases		SIR (95% CI)
			Observed	Expected	
1986	93,819	1,337,478	148	40.5	3.65 (3.07–4.24)
1987	24,818	393,025	31	11.1	2.79 (1.81–3.78)
1988–1990	21,012	310,685.5	17	9.4	1.81 (0.95–2.67)
Subtotal 1986–1990	139,649	2,041,188.5	196	61.0	3.21 (2.76–3.66)
Unknown	11,813	95,220.5	20	3.4	5.88 (3.30–8.46)
Total	150,813	2,136,409	216	64.4	3.35 (2.91–3.80)

In order to preliminarily estimate the dose-dependent risk of thyroid cancer in the cohort, and to calculate possible contribution of the radiation factor into the incidence rate, the doses to thyroid were assessed in two alternative ways using different sources of raw dosimetric data.

According to the first approach, the official dose records (ODR), which are available in SRU and were published in the UNSCEAR 2008 report [10] were used as a starting point for dose estimation. These whole-body doses were adjusted for known bias [30] and converted to doses for thyroid using the relevant conversion coefficients established by International commission on Radiological Protection (ICRP) [31].

Alternative thyroid dose assessment was based on the average RADRUE red bone marrow doses estimated in cleanup workers [16,17]. Red bone marrow doses available for 1000 study subjects were converted to thyroid doses, also utilizing aforesaid ICRP conversion coefficients. In both approaches the air kerma was used as intermediate reference value (i.e., whole body or red bone marrow doses were first converted to air kerma and then to thyroid doses). Excessive absolute risk—per 10,000 person-years, Gray (EAR/10^4Gy), according to alternative dose assessment options, was estimated to be in a range from 1.86 (95% CI: 0.47–3.24) to 2.07 (95% CI: 0.53–3.62). The excess relative risk per Gray (ERR/Gy) ranged from 2.38 (95% CI: 0.60–4.15) to 2.66 (95% CI: 0.68–4.64) [29].

These estimates confirm the presence of a dependency between the radiation dose e and thyroid cancer in those exposed in adulthood. A more sophisticated NRCRM–NCI thyroid cancer case-control study nested in the cohort of 150,813 male Chornobyl cleanup workers is at the final stage of accomplishment. The field work including subject tracing and interviewing, dose reconstruction, as well as statistical risk analysis has been finalized. New estimates of the thyroid cancer risk in cleanup workers will be obtained soon.

In general, the NRCRM and NRCRM–NCI studies demonstrate radiation risks of thyroid cancer in cleanup workers and are in line with both A-bomb survivors and the studies coordinated by the International Agency for Research on Cancer (IARC) (Table 3).

Table 3. Cancer risks in Ukrainian Chornobyl cleanup workers in comparison with other studies.

Study Group, Country, Reference	Type of Study, Cohort Size	Follow Up Time Period	Number of Cases(/Controls)	Risks
Leukemia (All types) C91–C95				
Chornobyl clean-up workers, Ukraine [24]	Case-control	1986–2000	71/501	ERR Gy^{-1} 3.44 (0.47–9.78; $p < 0.01$)
[25]	Case-control	1986–2006	137/863	ERR Gy^{-1} 2.38 (95% CI: 0.49–5.87; $p < 0.04$)
Leukemia (CLL excluded) C91.0, C92–C95				
Chornobyl cleanup workers, Russia [32]	Cohort 53,772	1986–1997	51	ERR Gy^{-1} 4.98 (95% CI: 0.59–14.47)
		1998–2007	60	−1.64 (95% CI: −2.55 to 0.57)
Life Span Study cohort, Japan [4]	Cohort 113,011	1950–2001	312	ERR Gy^{-1} 4.7 (95% CI: 3.3–6.5)
Chornobyl cleanup workers, Russia, Belarus, Baltic countries [18]	Case-control	1990–2000	19/83	ERR 0.1 Gy^{-1} 0.50 (90% CI: −0.38 to 5.7)
Chronic lymphocytic leukemia C91.1–C91.4				
Chornobyl cleanup workers, Ukraine [25]	Case-control	1986–2006	65	ERR Gy^{-1} 2.58 (95% CI: 0.02–8.43)
Chornobyl cleanup workers, Ukraine [33]	Cohort, 152,520	1987–2012	146	SIR 1.44 (95% CI: 1.21–1.68)
Multiple myeloma (C90)				
Chornobyl cleanup workers, Ukraine [34]	Cohort, 152,520	1996–2013	69	SIR 1.38 (95% CI: 1.06–1.71)
A-bomb survivors [4]	Cohort study, 113,011	1950–2001	136, including 31 not exposed	ERR Gy^{-1} 0.38 (95% CI: −0.23 to 1.36), $p = 0.21$
All solid cancers (C00-C80)				
Ukrainian cleanup workers of 1986–1987 [35]	Descriptive 84,599	1994–2013	11,116	SIR 107.5 (95% CI: 105.4–109.6)
		1994–2014	11,666	SIR 106.9 (95% CI: 105.0–108.9)
A-bomb survivors [2]	Cohort 105,427	1958–2008	17,448	35% per Gy (90% CI 28%; 43%) increase for men; 58% per Gy (43%; 69%) increase for women
Female breast cancer (C50)				
Ukrainian cleanup workers of 1986–87 [35]	Descriptive 11,300	1994–2013	336	SIR 157.8 (95% CI: 141.0–174.7)
		1994–2014	351	SIR 156.7 (95% CI: 140.3–173.1)
A-bomb survivors [2]	Cohort 105,427	1958–1998	1073	ERR Gy^{-1} 0.87 (90% CI: 0.55–1.30)
Thyroid cancer (C73)				
A-bomb survivors [2]	Cohort 105,427	1958–1998	471	ERR Gy^{-1} = 0.57 (90% CI: 0.24–1.10)
Cleanup workers [36]	Case-control	Russia: 1993–1998; Belarus: 1993–2000; Baltic: 1990–2000	107/423	ERR per 100 mGy = 0.38 (95% CI: 0.10–1.09)
Ukrainian Cleanup workers [28]	Cohort: 150,813;	1986–2010	196	SIR = 3.50 (95% CI: 3.04–4.03)
[29]	Cohort: 150,813;	1986–2012	216	ERR Gy^{-1} from 2.38 (95% CI: 0.60–4.15) to 2.66 (95% CI: 0.68–4.64)

The last UNSCEAR analysis has shown that the total number of cases of thyroid cancer registered in the period 1991−2015 in males and females, who were under 18 in 1986 (for the whole of Belarus and Ukraine, and for the four most contaminated oblasts of the Russian Federation), approached 20,000, and basically increased monotonically over the period of 2006−2015. The observed increase in the incidence of thyroid cancer is attributable to a variety of factors: Increased spontaneous incidence rate with aging of the birth cohort, radiation exposure, awareness of thyroid cancer risk after the accident, and improvement of diagnostic methods to detect thyroid cancer. The committee estimated that the fraction of the incidence of thyroid cancer attributable to radiation exposure is of the order of 0.25, with the uncertainty range of the attributable fraction extending at least from 0.07 to 0.5. In the opinion of the committee, the increased incidence of thyroid cancer after the Chornobyl accident is a major issue and needs further investigation to determine the long-term consequences of radiation exposure [37].

The studied postaccidental period demonstrated an increase in rates of "early" cancer types—thyroid, breast, and leukemia. Based on the experience of A-bomb survivors, cohort cancer rates in the studied cohorts will remain elevated due to aging and differences in radiation risks for specific cancer types. Hence, malignant disease monitoring is still an actual task of medical surveillance for the exposed cohorts.

Pathology of Cancers in Radiation Exposed Population after Chornobyl

The first results from the radiation-induced cancers pathology were obtained in thyroid cancer, urinary bladder cancer, breast cancer, and leukemia. Attempts were done to find radiation specific cancer markers, but to date these have not been successful. Similar types of point mutations were described in different cancers, supposing the contributive role of radiation exposure (*BRAF*, *MAPK38*, *RAS*) [38,39].

Studies of leukemia have not demonstrated specific pathologic features of radiation-induced myelogenous and acute leukemia. As epidemiologic studies of cleanup workers have shown, regarding radiation risks of chronic lymphocytic leukemia, there was an interest in finding the specific features of radiation-induced CLL. A special substudy was performed on clinical and morphological features of CLL in the cleanup workers (80) in comparison with nonexposed CLL cases (70). The shorter period of white blood cell doubling in peripheral blood (10.7 vs. 18.0; $p < 0.001$), frequent infectious episodes, lymphadenopathy and hepatosplenomegaly (37 vs. 16), higher expression for CD38, and lower for ZAP-70 antigens were among the peculiarities, although not statistically significant.

Higher frequencies (89.3%) of unmutated immunoglobulin variable heavy chain (IGHV) genes were shown among 28 cleanup workers from 1986 with CLL, in comparison with 68.1% in 238 nonexposed CLL patients. In a later study, the same group of investigators failed to demonstrate any difference [40]. Comparison of genome changes in general exposed population vs. nonexposed one in the post-Chornobyl period describes upregulation of *MYC*, *HNF1A*, and *HNF4A* and *YWHAG*, *NF-κB1*, and *SP1*, together with a downregulation of *CEBPA*, *YWHAG*, *SATB1*, and *RB1* [41].

A further CLL cleanup workers study of 17 CLL cases from the cohort showed more frequent mutations in the telomere maintenance pathway genes POT1 and ATM, compared with 28 unexposed CLL patients from Ukraine and 100 from the USA. Tumor telomere length was significantly longer in cleanup workers and was associated with the *POT1* mutation and survival [42].

The performed molecular studies suggest the presence of a changed gene profile after exposure that could form a background for later effects, especially cancers. A statistically significant and dose-dependent decrease in expression of the *BCL2*, *SERPINB9*, *CDKN2A*, and *STAT3* genes was demonstrated in parallel to a dose-dependent overexpression of *MCF2L* and upregulation of *TP53* (up to 100 mSv). *IL1B* expression was the highest in exposed doses from 0.1 to 100 mSv with a negative correlation between at IL1B expression and CD19+3−, CD3-HLA-DR+, CD4+8− cell counts, and CD4+/CD8+ ratio. Hyper expression of *TNF* gene in doses above 100 mSv to 1,000 mSv was shown, and in higher doses a combination of *TNF* downregulation with an increase in *IFNG* gene expression were demonstrated with correlations with numbers of CD3+16+56+ and CD25+ lymphocytes, and

inhibition of expression of *CLSTN2*. An increased expression of γ-H2AX and Cyclin D1 correlated to radiation dose, telomere shortening to age, and concomitant pathology.

5. Conclusions

Thirty years after the Chornobyl accident an excess was demonstrated in incidences of the "early" cancers—thyroid, breast, and leukemia, with a slight tendency to decrease at a later period. Dose dependency was shown for thyroid cancer and leukemia, and surprisingly radiation risks of chronic lymphocytic leukemia. For breast cancer incidence there are indications of an increase, but none of analytical case-control studies are available in cleanup workers and the general exposed population. Summarizing the incidence rates and risks, it should be stated that observed tendencies, dynamics, and risks magnitude are different for the malignancies of different localizations and consistent with those for other exposed populations.

The performed studies demonstrate the possibility of understanding the nature of radiation-induced effects after low-dose exposure. Genome instability, including elevated micronuclei counts, gamma-H2AX expression, telomere length variability, and changes in gene expression, could serve as background for low-dose health effects. To connect possible late effects, such as specific subtypes of radiogenic cancers, with radiation exposure, the analytical cohort and case-control studies need to include biomarkers of dose and disease supplemented by a uniform dosimetry.

Since the solid cancer risks in the studied cohorts supposedly have not been realized completely, the monitoring and registers for support are still an actual task of medical follow-up.

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ВИСНОВКИ.

У дисертаційній роботі представлені результати ретельно спланованих досліджень, спрямованих на достовірну оцінку реалізованих ризиків стохастичних ефектів опромінення серед ліквідаторів в Україні на основі розроблених методичних засад великомасштабного аналітичного епідеміологічного дослідження.

- Запровадження науково обгрунтованих методів проведення аналітичних епідеміологічних досліджень для вивчення стохастичних ефектів опромінення після аварії на ЧАЕС дозволило сформувати інформаційну базу таких досліджень в Україні та визначити дозозалежні ризики виникнення лейкемії серед учасників ліквідації наслідків аварії.
    - За результатами проведених аналітичних епідеміологічних досліджень вперше серед учасників ліквідації наслідків аварії на ЧАЕС в Україні було визначено достовірну лінійну позитивну асоціацію між кумулятивною дозою опромінення на червоний кістковий мозок з надлишком відносного ризику виникнення лейкемії на 1 Грей опромінення (ERR/Gy), який в 1986 – 2000 рр склав 3.44 (95 % довірчий інтервал: 0.47–9.78, $p<0,01$), а впродовж 1986–2006 рр. – 2,38 з 95 % ДІ від 0,49 до 5,87 та $p=0,004$;
- Вперше було визначено позитивну дозозалежну асоціацію ризиків виникнення хронічної лімфоцитарної лейкемії впродовж 1986-2006 рр. серед ліквідаторів в Україні (ERR/Gy=2,58, 95% довірчий інтервал 0,02–8,43 і $p=0,047$).
- Вперше було визначено суттєвий вплив професійного контакту із бензином на надмірний ризик виникнення мієлоїдної лейкемії,

переважно, за рахунок її хронічної форми. Співвідношення шансів (OR) склало 3,48, 95% довірчий інтервал: 1,09–11,12.

- Перші висновки аналітичного дослідження свідчать про збільшення ризику раку ЩЗ серед УЛНА на ЧАЕС, хоча із статистично граничною значущістю ((ERR/Gy)=0.40; 95% довірчий інтервал: -05–1.48; p=0.12).
- Встановлено, що Державний реєстр України осіб, які постраждали внаслідок аварії на Чорнобильській АЕС (ДРУ), є прийнятним джерелом інформації для створення когорти учасників ліквідації наслідків аварії для проведення аналітичних епідеміологічних досліджень, а також альтернативним джерелом даних щодо випадків досліджуваних захворювань
- Визначено відповідність обраних методів аналітичної ретроспективної реконструкції індивідуальних доз опромінення критеріям використання в аналітичних епідеміологічних дослідженнях (методу RADRUE для оцінки доз зовнішнього опромінення на червоний кістковий мозок, на щитоподібну залозу та на гонади в дослідженні трансгенераційних генетичних ушкоджень, комплексу аналітичних методик для визначення дози внутрішнього опромінення на щитоподібну залозу і гонади) і визначено способи забезпечення анкетування для отримання необхідних даних.
- Використання альтернативних джерел інформації забезпечило ідентифікацію досліджуваних захворювань у повному обсязі, що є необхідною складовою достовірних оцінок ризиків виникнення стохастичних ефектів. В перелік запропонованих для використання джерел входять реєстр лейкемії, створений за даними територіальних медичних установ, Національний канцер-реєстр, Державний реєстр України осіб, які постраждали внаслідок аварії на Чорнобильській АЕС.

- Для забезпечення якості аналітичних оцінок ризиків стохастичних ефектів опромінення необхідною ланкою дослідження є верифікація діагнозів, для якої запоропоновано технологію проведення незалежної міжнародної діагностичної експертизи. Вперше в Україні було проведено чотири сесії такої експертизи для верифікації діагнозів лейкемії у випадках, включених до аналізу ризиків.
- Ідентифікація і подальше простежування випадків захворювання в аналітичному епідеміологічному дослідженні дозволяють вивчати і статистично оцінювати особливості перебігу хвороби серед опромінених осіб.
- Аналіз особливостей клінічного перебігу випадків ХЛЛ вперше визначив достовірно вищий ризик смерті у осіб, опромінених у дозі, вищій за 22 mGy порівняно із опроміненими в дозі, нижчій за цей рівень. Виживаність була коротшою серед випадків ХЛЛ, опромінених в більш молодому віці, вищим рівнем лімфоцитозу, та старшим віком при встановленні діагнозу ($p < 0.05$).
- Дослідження генетичних ушкоджень серед опромінених осіб є перспективним напрямом досліджень етіології та перебігу захворювань. Серед хворих ліквідаторів не було встановлено збільшеного числа мутацій в ХЛЛ-асоційованих генах порівняно із неопроміненими особами.
- Вперше на основі використання новітніх генетичних та епідеміологічних методів було доведено відсутність на поточний момент спадкових генетичних ушкоджень у дітей, народжених від батьків, опромінених внаслідок участі в ЛНА на ЧАЕС, або в процесі евакуації.

Додаток А. СПИСОК ОПУБЛІКОВАНИХ ПРАЦЬ ЗА ТЕМАТИКОЮ ДИСЕРТАЦІЇ.

Наукові праці, в яких опубліковані основні наукові результати дисертації

Статті (фахові видання, віднесені до першого і другого квартилів (Q1 і Q2) відповідно до класифікації SCImago Journal and Country Rank або Journal Citation Reports)

1. Cardis E., Howe G., Ron E., Bebeshko V., Bogdanova T., Bouville A., Carr Z., Chumak V., Cardis E., Howe G., Ron E., Bebeshko V., Bogdanova T., Bouville A., Carr Z., Chumak V., Davis S., Demidchik Y., Drozdovitch V., Gentner N., **Gudzenko N.,** Hatch M., Ivanov V., Jacob P., Kapitonova E., Kenigsberg Y., Kesminiene A., Kopecky K. J., Kryuchkov V., Loos A., Pinchera A., Reiners C., Repacholi M., Shibata Y., Shore R. E., Thomas G., Tirmarche M., Yamashita S., Zvonova I. Cancer consequences of the Chernobyl accident: 20 years on // Journal of Radiological Protection. 2006. Vol. 26 (2). P. 127–140.

https://doi.org/10.1088/0952–4746/26/2/001

Систематизація даних для дескриптивного аналізу поширеності і захворюваності на злоякісні новоутворення контингентів осіб, постраждалих внаслідок Чорнобильської катастрофи в Україні

2. Prysyazhnyuk A., Romanenko A., **Gudzenko N.**, Fuzik M. and Fedorenko Z. Thyroid cancer in Ukrainian population groups affected by the Chernobyl accident // Data Science Journal. – 2009. Vol. 8 (79). – BR6–BR12. https://doi.org/10.2481/dsj.BR–03

Підготовка бази даних для аналізу за групами постраждалих, контроль якості даних, дескриптивний аналіз даних, участь у підготовці рукопису.

3. Fuzik M., Prysyazhnyuk A., Shibata Y., Romanenko A., Fedorenko Z., Gulak L., Goroh Y., **Gudzenko N.**, Trotsyuk N., Khukhrianska O., Saenko V.,

Yamashita S. Thyroid cancer incidence in Ukraine: trends with reference to the Chernobyl accident // Radiat Environ Biophys. 2011. Vol. 50. P. 47–55.

https://doi.org/10.1007/s00411–010–0340–y

Розрахунки SIR, участь у написанні рукопису, обговорення, редагування

4. Dyagil I., Adam M., Beebe G. W., Burch J. D., Gaidukova S. N., Gluzman D., **Gudzenko N.**, Klimenko V., Peterson L., Reiss R. F., Finch S. C. Histologic Verification of Leukemia, Myelodysplasia,and Multiple Myeloma Diagnoses in Patients in Ukraine, 1987–1998 // International Journal of Hematology. 2002. Vol. 76. P. 55–60. https://doi.org/10.1007/BF02982719

Участь у формуванні ідеї і шляхів її реалізації, розробка форм поточного і заключного документування результатів, узагальнення і аналіз результатів, участь у підготовці рукопису для публікації.

5. Romanenko A., Bebeshko V., Hatch M., Bazyka D., Finch S., Dyagil I., Reiss R., Chumak V., Bouville A., **Gudzenko N.**, Zablotska L., Pilinskaya M., Lyubarets T., Bakhanova E., Babkina N., Trotsiuk N., Ledoschuk B., Belayev Y., Dybsky S. S., Ron E., Howe G. Ukrainian-–American study of leukemia and related disorders among Chornobyl cleanup workers from Ukraine: I.Study Methods // Radiation Research. 2008. Vol. 170. P. 691–697.

https://doi.org/10.1667/RR1402.1

Систематизація даних, контроль якості даних, участь в дескриптивному аналізі даних

6. Chumak V. V., AYe Romanenko A. Ye., Voillequé P. G., Bakhanova E. V. , **Gudzenko N.**, Hatch M., Zablotska L. B., Golovanov I. A., Luckyanov N. K. , Sholom S. V., Kryuchkov V. P., Bouville A. Ukrainian–American study of leukemia and related disorders among Chornobyl cleanup workers from Ukraine: II. Estimation of bone–marrow doses // Radiation Research. 2008 Vol. 170. P. 698 – 710.

https://doi.org/10.1667/RR1403.1

Організація простежування, контакту і анкетування суб'єктів дослідження для отримання дозозалежної інформації, систематизація даних, контроль якості даних (епідеміологічна складова)

7. Romanenko A. Ye., Zablotska L. B., Finch S., Hatch M., Lubin J., Bebeshko V. G., Bazyka D. A., **Gudzenko N.,** Dyagil I. S., Reiss R., Bouville A., Chumak V. V., Belyaev Y., Masnyk I., Ron E., Howe G. R. Ukrainian–American study of leukemia and related disorders among Chornobyl cleanup workers from Ukraine: III.Radiation risks // Radiation Research. 2008. Vol. 170. p. 711 – 720. https://doi.org/10.1667/RR1404.1

Систематизація даних, поточний та заключний контроль якості даних, формування аналітичної бази даних, участь в проведенні аналізу дозо залежних ризиків.

8. Zablotska L. B.,, Bazyka D., Lubin J. H., **Gudzenko N.**, Little M. P., Hatch M., Finch S., Dyagil I., Reiss R. F., Chumak V. V., Bouville F., Drozdovitch V., Kryuchkov V. P., Golovanov I., Bakhanova E., Babkina N., Lubarets T., Bebeshko V., Romanenko A., Mabuchi K. Radiation and the risk of chronic lymphocytic and other leukemias among Chornobyl cleanup workers // Environ Health Perspect. 2013. Vol. 121, № 1. P. 59–65.

https://doi.org/10.1289/ehp.1204996

Систематизація даних, контроль якості даних, участь в аналізі даних, участь в підготовці рукопису

9. Ostroumova E., **Gudzenko N.**, Brenner A., Gorokh Y., Hatch M., Prysyazhnyuk A., Mabuchi K., Bazyka D. Thyroid cancer incidence in Chornobyl liquidators in Ukraine: SIR analysis, 1986–2010 // European Journal of Epidemiology. 2014, April. P.337–342.

https://doi.org//10.1007/s10654–014–9896–1

Систематизація даних, участь в дескриптивному аналізі даних, підготовці рукопису

10. **Gudzenko N**., Hatch M., Bazyka D., Dyagil I., Reiss R.F., Brenner A., Chumak V., Babkina N., Zablotska L. B., Mabuchi K. Non–radiation risk factors for leukemia: A case-–control study among Chornobyl cleanup workers in Ukraine // Environmental research. 2015. Vol. 140. P. 72–76.

https://doi.org//10.1016/j.envres.2015.06.019

Ідея дослідження, участь в статистичному аналізі даних, участь в підготовці рукопису

11. Finch S. C., Dyagil I., Reiss R. F., **Gudzenko N.**, Babkina N., Lyubarets T., Bebeshko V., Romanenko A., Chumak V. V., Bouville A., Hatch M., Little M. P., Bazyka D., Zablotska L. B. Clinical characteristics of chronic lymphocytic leukemia occurring in Chornobyl cleanup workers // Hematological Oncology. 2017. Vol. 35 (2). P. 215–224. DOI: 10.1002/hon.2278

https://doi.org//DOI:10.1002/hon.2278

Поточний і заключний контроль якості даних, формування аналітичної бази даних, участь в статистичному аналізі клінічних особливостей

12. Ojha J., Dyagil I., Finch S. C., Reiss R. F., de Smith A. J., Gonseth S., Zhou M., Hansen H. M., Sherborne A. L., Nakamura J., Bracci P. M., **Gudzenko N.**, Hatch M., Babkina N., Little M. P., Chumak V. V., Walsh K. M., Bazyka D., Wiemels J. L. and Zablotska L. B. Genomic characterization of chronic lymphocytic leukemia (CLL) in radiation exposed Chornobyl cleanup workers // Environmental Health. 2018. Vol. 17. P. 43.

https://doi.org/10.1186/s12940-018-0387-9

Формування і характеристика досліджуваних груп, участь в аналізі даних (епідеміологічна складова), підготовка публікації

13. Bazyka D., **Gudzenko N.**, Dyagil I., Ilienko I., Belyi D., Chumak V., Prysyazhnyuk A., Bakhanova E. Cancers after Chornobyl: From epidemiology to molecular quantification // Cancers. 2019. Vol. 11. P. 1291.

https://doi.org/10.3390/cancers11091291

Статистичний аналіз даних щодо захворюваності на злоякісні новоутворення, участь в підготовці рукопису

14. Bazyka D., Hatch M., **Gudzenko N.**, Cahoon E. K., Drozdovitch V., Little M. P., Chumak V., Bakhanova E., Belyi D., Kryuchkov V., Golovanov I., Mabuchi K., Illienko I., Belayev Y., Bodelon C., Machiela M. J., Hutchinson A., Yeager M., Berrington de Gonzalez A., Chanock S. J. Field study of the possible effect of parental irradiation on the germline of children born to cleanup workers and evacuees of the Chornobyl Accident // Am. J. Epidemiol.2020 Vol. 189, № 12. P. 1451–1460. https://doi.org/10.1093/aje/kwaa095

Формування досліджуваних груп, вибір використаних методів дослідження, формування бази даних, контроль якості даних, участь в аналізі

15. Yeager M., Machiela M J., Kothiyal P., Dean M., Bodelon C., Suman S., Wang M., Mirabello L., Nelson C. W., Zhou W., Palmer C., Ballew B., Colli L. M., Freedman1 N. D., Dagnall C., Hutchinson A., Vij V., Maruvka Y., Hatch M., Illienko I., Belayev Y., Nakamura N., Chumak V., Bakhanova E., Belyi D., Kryuchkov V., Golovanov I., **Gudzenko N**., Cahoon E. K., Albert P., Drozdovitch V., Little M. P., Mabuchi K., Stewart C., Getz G., Bazyka D., Berrington de Gonzalez A., Chanock S. J. Lack of transgenerational effects of ionizing radiation exposure from the Chernobyl accident // Science. 2021. Vol. 372, Issue 6543. P. 725–729. https://doi.org/10.1126/science.abg2365

Формування досліджуваних груп, забезпечення простежування, анкетування, контроль якості даних, участь в аналізі і підготовці публікації

Інші статті (фахові видання, віднесені до третього квартилю (Q3) відповідно до класифікації SCImago Journal and Country Rank або Journal Citation Reports)

16. Chumak V., Drozdovitch V., Kryuchkov V., Bakhanova E., Babkina N., Bazyka D., **Gudzenko N**., Hatch M., Trotsuk N, Zablotska L., Golovanov I., Luckyanov N., Voillequé P., Bouville A. Dosimetry Support of the Ukrainian-–American Case–control Study of Leukemia and Related Disorders Among Chornobyl Cleanup Workers // Health Physics. 2015. Vol. 109. Issue. P. 296–301. https://doi.org/10.1097/HP.0000000000000341

Організація простежування, контакту і анкетування суб'єктів дослідження систематизація даних, контроль якості даних (епідеміологічна складова)

17. Bazyka D., Dyagil I., **Gudzenko N**., Goroh E., Polyschuk O., Trotsuk N., Babkina N., Romanenko A. Chronic Lymphocytic Leukemia in Chornobyl Cleanup Workers // Health Physics. 2016.– Vol 111 (2). P. 186–191.

https://doi.org/10.1097/HP.0000000000000440

Формування і ведення бази даних, контроль якості даних, участь в аналізі даних, участь в підготовці рукопису.

19. Bazyka D., Prysyazhnyuk A., **Gudzenko N.**, Dyagil I., Belyi D., Chumak V., and Buzunov V. Epidemiology of late health effects in Ukrainian Chornobyl cleanup workers // Health Physics. 2018. N. 115 (1). P. 161–169.

https://doi.org/10.1097/HP.0000000000000440

Участь у статистичниому аналізі даних щодо захворюваності на злоякісні новоутворення, підготовка рукопису до публікації

20. Drozdovitch V., Kryuchkov V., Bakhanova E., Golovanov I., Bazyka D., **Gudzenko N.**, Trotsyuk N., Hatch M., Cahoon E.K., Mabuchi K., Bouville A., Chumak V. Estimation of radiation doses for a case-–control study of Thyroid cancer among Ukrainian Chernobyl cleanup workers // Health Physics. 2020. Vol. 118. N. 1. P. 18–35. https://doi.org/10.1097/HP.0000000000001120

Організація простежування, контакту і анкетування суб'єктів дослідження, систематизація і контроль якості даних (епідеміологічна складова), участь у підготовці рукопису.

Статті (фахові видання), віднесені до четвертого квартилю (Q4) відповідно до класифікації SCImago Journal and Country Rank або Journal Citation Reports)

21. Bazyka D. A., **Gudzenko N. A.**, Dyagil I. S., Babkina N. G., Chumak V. V., Bakhanova E. V., Paramonov V. V., Romanenko A. Ye. Multiple myeloma among Chornobyl accident clean–up workers. State and perspectives of analytical study // Проблеми радіаційної медицини та радіобіології. 2013. Вип. 18. С 169–172. ISSN 2313–4607

Ідея, аналіз даних, участь у підготовці рукопису.

22. Присяжнюк А. Є., Базика Д. А., Романенко А. Ю., **Гудзенко Н. А.**, Фузік М. М., Троцюк Н. К., Федоренко З. П., Гулак Л. О., Сліпенюк К. М., Бабкіна Н. Г., Хухрянська О. М., Горох Є.Л. Чверть століття після

Чорнобильської аварії: ризик раку в групах постраждалого населення – *Проблеми радіаційної медицини та радіобіології*. 2014. Вип. 19. С.111 – 122.

ISSN 2313-4607

Участь в узагальненні даних описових і аналітичних досліджень онкологічних захворювань в групах осіб, які постраждали внаслідок аварії на ЧАЕС, аналізі даних, підготовці рукопису до публікації

23. Bazyka D., Gudzenko N., Dyagil I., Trotsiuk N., Gorokh E., Fedorenko Z., Chumak V., Bakhanova E., Ilienko I., Romanenko A. Incidence of multiple myeloma among cleanup workers of the Chornobyl accident and their survival // Exp Oncol. 2016. Vol. 38 (4). P.267–271. http://dspace.nbuv.gov.ua/handle/123456789/137696

Створення і ведення бази даних щодо випадків множинної мієломи, SIR аналіз захворюваності

24. Присяжнюк А., Троцюк Н., **Гудзенко Н.А.**, Чумак В., Фузік М., Беляєв Ю., Базика Д., Федоренко З. та ін. Радіаційні ризики раку щитовидної залози в учасників ліквідації аварії на ЧАЕС на базі альтернативних оцінок доз // Проблеми радіаційної медицини та радіобіології. 2018. С. 200–215.

ISSN 2313-4607

Систематизація даних, участь в аналізі даних, підготовці рукопису до публікації

Наукові праці, які засвідчують апробацію матеріалів дисертації (тези доповідей і матеріали конференцій)

1. Ледощук Б.А. Троцюк Н.К., Хухрянская Е.Н., Гудзенко Н.А. Государственный регистр Украины пострадавших в результате Чернобыльской катастрофы – информационная база для обеспечения эпидемиологических исследований последствий Чернобыльской катастрофы Матер. III Междунар. симпозиум «Хроническое радиационное воздействие: медико–биологические эффекты» Челябинск, 24–26 октября 2005. С.154.

2. Романенко А.Ю., Ледощук Б.О. **Гудзенко Н.А.** Інформативність Державного реєстру України осіб, які постраждали внаслідок Чорнобільської катастрофи, для медичного моніторингу учасників ліквідації наслідків аварії Двадцять років Чорнобільської катастрофи Погляд у майбутнє: Зб. тез. міжнар. конф. Київ 24–26 квітня 2006р. К., 2006. С. 80–81.

3. Бебешко В.Г., Дягіль І.С, **Гудзенко Н.А**. Створення системи експертизи онкогематологічних захворювань як основи для достовірної оцінки ризиків лейкемії серед постраждалих внаслідок Чорнобильської катастрофи Двадцять років Чорнобільської катастрофи Погляд у майбутнє: Зб. тез. міжнар. конф. Київ 24–26 квітня 2006р. К., 2006. С. 80–81.

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