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Risk of hematological malignancies among Chernobyl liquidators

Ausrele Kesminiene¹, Anne-Sophie Evrard¹, Viktor K. Ivanov², Irina V. Malakhova³, Juozas Kurtinaitis⁴, Aivars Stengrevics⁵, Mare Tekkel⁶, Lynn R. Anspaugh⁷, André Bouville⁸, Sergei Chekin², Vadim V. Chumak⁹, Vladimir Drozdovitch⁸, Vladimir Gapanovich¹⁰, Ivan Golovanov¹¹, Phillip Hubert¹², Sergei V. Illichev¹³, Svetlana E. Khait², Viktor P. Krjuchkov¹¹, Evaldas Maceika¹⁴, Marat Maksyoutov², Anatoly K. Mirkhaidarov¹⁵, Semion Polyakov³, Natalia Shchukina², Vanessa Tenet¹, Tatyana I. Tserakhovich³, Aleksandr Tsykalo¹⁶, Aleksandr R. Tukov¹¹, and Elisabeth Cardis^{1,17}

¹ International Agency for Research on Cancer, Lyon, France

² Medical Radiological Research Centre of Russian Academy of Medical Sciences (MRRC RAMC), Obninsk, the Russian Federation

³ Republican Scientific-and Practical Center for Medical Technologies, Informatization, Administration and Management of Health (RNPC MT), Minsk, Belarus

⁴ Institute of Oncology, Vilnius, Lithuania

⁵ Latvian Centre of Oncology, Riga, Latvia

⁶ National Institute for Health Development, Tallinn, Estonia

⁷ Radiobiology Division, Department of Radiology, University of Utah, Salt Lake City, Utah, USA

⁸ US National Cancer Institute, NIH/NCI/DCEG, Rockville, MD, USA

⁹ Scientific Centre for Radiation Medicine, Kiev

¹⁰ Research Institute of Haematology and Blood Transfusion (RIHBT), Minsk, Belarus

¹¹ Institute of Biophysics (IB), Moscow, The Russian Federation

¹² Direction des Risques Chroniques, Institut National de l'Environnement Industriel et des Risques (INERIS), Verneuil-en-Halatte, France

¹³ National Nuclear Energy Generation Company (NNEGC) "ENERGOATOM", Ukraine

¹⁴ Institute of Physics, Vilnius, Lithuania

¹⁵ Republican Scientific Centre of Radiation Medicine and Human Ecology, Gomel, Belarus

¹⁶ Department of Dose Reconstruction, Chernobyl Nuclear Power Plant, Chernobyl, Ukraine

^aCorrespondence and reprint requests should be addressed to: Prof Elisabeth Cardis, International Agency for Research on Cancer, 150 Cours A. Thomas, 69372 Lyon, France, Phone number: +33 4 72 73 85 08; Fax: +33 4 72 73 84 51, cardis@iarc.fr.

¹⁷Now at: Center for Research in Environmental Epidemiology (CREAL), Barcelona, Spain

^bSubjects who were smokers and for whom it was not possible to determine whether they had quit smoking before the reference date are included as current smoker in this analysis – results including these subjects as ex-smokers are very similar.

Ethics

The study was approved by the IARC Ethical Review Committee, the Belarus Coordinating Council for Studies of the Medical Consequences of the Chernobyl Accident, the Ethical Committee of the Medical Radiological Research Centre of the Russian Academy of Medical Sciences, Obninsk, the Ethical Review Board of the Institute of Oncology, Vilnius, Lithuania; the Ethical Review Committee of Latvian Oncology Center; the Tallinn Medical Research Ethics Committee. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 1983.

Abstract

A case-control study of hematological malignancies was conducted among Chernobyl liquidators (accident recovery workers) from Belarus, Russia and Baltic countries in order to assess the effect of low-to-medium dose protracted radiation exposures on the relative risk of these diseases. The study was nested within cohorts of liquidators who had worked in 1986–87 around the Chernobyl plant. 117 cases (69 leukemia, 34 non-Hodgkin Lymphoma (NHL) and 14 other malignancies of lymphoid and hematopoietic tissue) and 481 matched controls were included in the study. Individual dose to the bone marrow and uncertainties were estimated for each subject. The main analyses were restricted to 70 cases (40 leukemia, 20 NHL and 10 other) and their 287 matched controls with reliable information on work in the Chernobyl area. Most subjects received very low doses (median 13 mGy). For all diagnoses combined, a significantly elevated OR was seen at doses of 200 mGy and above. The Excess Relative Risk (ERR) per 100 mGy was 0.60 (90% confidence interval (CI): -0.02, 2.35). The corresponding estimate for leukemia excluding chronic lymphoid leukemia (CLL) was 0.50 (90%CI -0.38, 5.7). It is slightly higher than, but statistically compatible with, those estimated from a-bomb survivors and recent low dose-rate studies. Although sensitivity analyses showed generally similar results, we cannot rule out the possibility that biases and uncertainties could have led to over or underestimation of the risk in this study.

Introduction

The carcinogenic effects of ionizing radiation at moderate to high doses are well documented. Current estimates of cancer risk associated with external exposure to low linear energy transfer (LET) ionizing radiation are derived from studies of groups exposed primarily at high dose rates, in particular the survivors of the atomic bombings in Hiroshima and Nagasaki and patients irradiated for therapeutic purposes (1–2). Radiation protection recommendations, however, have generally been based on the use of these estimates in conjunction with uncertain models to extrapolate effects to the relatively low-dose, low dose-rate exposures of environmental and occupational concern, and across populations with different baseline cancer risks (2–3).

Direct estimates of the carcinogenic effects of protracted low-level radiation exposure in humans have been derived recently in a 15-country study of cancer risk among workers in the nuclear industry (4–5) as well as in a study of cancer risk among persons living along the Techa River in the Urals (6–7). Results from these studies suggest a small excess risk of cancer, even following low doses and dose-rates. Both studies, however, have limitations: in the 15-country study, the exact magnitude of smoking confounding is not clear and it is difficult to evaluate the risk estimates one would obtain in the absence of confounding. In the Techa River study, errors in the dose estimates may have led to overestimation of the risk. Further studies of populations receiving relatively low doses at different dose rates are therefore needed to confirm these findings.

The Chernobyl accident, which occurred on 26 April 1986, exposed millions of people in Belarus, the Russian Federation and Ukraine to widespread radioactive contamination at different dose-rates and dose levels. The majority of exposed persons received low doses. The Chernobyl liquidators, or accident recovery workers, are of particular interest, as they tended to receive the higher doses through their work on the industrial site of the power plant and in surrounding areas. The average reported doses were of the order of 170 mGy in 1986 and decreased from year to year (8). In all, about 600,000 liquidators are thought to have participated in the clean up of the Chernobyl accident. Approximately 65% of these worked in 1986 or 1987 in the 30-km area around the power plant. They were mainly exposed to external γ and β radiation. Depending on the nature of their work, some liquidators received their dose in a matter of minutes or hours while others received it over months or even years.

The liquidators therefore form a unique group for the epidemiological study of the effects of exposure protraction in the low to medium dose range.

Leukemia (excluding chronic lymphoid leukemia, CLL) has been shown to be one of the cancers most strongly associated with radiation exposure (1–2). Furthermore, among radiation-induced malignancies, a relatively short latency is assumed for leukemia compared to most solid tumors (increases have been observed as early as two to five years after exposure). The results of studies of leukemia risk among liquidators are, however, inconclusive. A number of authors have reported increases in the incidence of leukemia among liquidators in Russia, Belarus and Ukraine (9–11) compared to the general population of these countries. These results must be interpreted with caution as they may be an artifact of the active medical surveillance system of exposed populations set-up after the accident, particularly in Russia and Ukraine where no systematic centralized population based cancer registry existed at the time of the accident (12). Smaller studies of Estonian, Latvian and Russian liquidators lack statistical power and provide little information about risks (13–16). An approximately two-fold increased risk was reported however in a very large cohort of liquidators in Russia with registered radiation doses between 150 and 300 mGy (17). Dose estimates were, however, quite uncertain in these studies.

A collaborative case-control study of hematological malignancies was therefore set-up, nested within cohorts of Belarus, Russian and Baltic countries liquidators, to evaluate the radiation-induced risk of these diseases among the liquidators. The study was based on a common protocol and detailed dose reconstruction was conducted in all countries. The current paper presents the findings of this study.

Methods

Study design

The study population consisted of the cohorts of approximately 66,000 Belarus, 65,000 Russian and 15,000 Baltic countries liquidators who took part in the clean-up activities on the reactor site and in the contaminated area around the Chernobyl nuclear power plant between 26 April 1986 and 31 December 1987 and were included in the Chernobyl Registry (in Belarus and Russia) or included in established Baltic liquidator cohorts (18). In Russia, for logistic reasons, the cohort was restricted to liquidators who resided in one of the following regions at the moment of registration: Northwest, Volgo-Vyatsky, Central-Chernozem, North-Caucasus, and Urals, as well as to the liquidators included in the Registry of professional radiation workers of the Institute of Biophysics (16). A roster of the study population was prepared by: the State Chernobyl Registry of the Republican Scientific and Practical Center for Medical Technologies, Informatization, Administration and Management of Health (RNPC MT), in Minsk, Belarus; the Russian National Medico-Dosimetry Registry (RNMDR), in Obninsk, Russia; the Cancer Registries of Latvia and Lithuania; and the National Institute for Health Development in Estonia.

The cases were defined as all histologically or cytologically verified cases of leukemia, NHL, myelodysplasia and myeloproliferative disease diagnosed in the study population during the study period: in 1993–1998 for Russia, 1993–2000 for Belarus and 1990–1998 for Baltic countries. Cases diagnosed before 1 January 1993 were not included in Russia and Belarus because it was unclear whether complete ascertainment could be achieved before that date. Furthermore, in Belarus, the study was restricted to cases diagnosed after 1992 to avoid re-interviewing cases diagnosed in 1991–92 since they were included in a pilot case-control study carried out by the same investigators. NHL was included in the study as the distinction between lymphoid leukemia and lymphoma can be artificial (19) and NHL includes a number of distinct diseases with different etiology and clinical manifestation; myelodysplasia and

myeloproliferative disease were included because of the haziness of diagnostic criteria with some forms of myeloid leukemia (19). Regardless of the definition of cases in the study protocol, in Belarus, local investigators also interviewed patients with multiple myeloma (MM). After verifying that ascertainment for MM cases was complete, it was decided to include them in the study, since the evidence with regard to a possible relationship with ionizing radiation is unclear (5-20-21). Moreover, this disease, like CLL and small lymphocytic lymphoma (SLL), belongs to the group of mature B-cell neoplasms. Cases were ascertained retrospectively either by computer linkage or manual comparison between the roster of the study population and the list of cases drawn from the National Cancer Registries in Belarus, Estonia, Latvia and Lithuania and the National Medical Dosimetry Registry in Russia as well as from the Registry of Hematological Disorders at the Research Institute of Hematology and Blood Transfusion (RIHBT) in Belarus. Prospective case ascertainment was conducted in Belarus and Russia from 1997 through the hematology and oncology departments of the oblast (administrative region) and central hospitals.

An international panel that consisted of Belarusian, Russian and Finnish pathologists and haematologists (KF, MSK, AS, LT) reviewed abstracted clinical records, bone marrow, peripheral blood and lymphoid tissue slides of the cases included in the study. WHO Classification of Tumours of the Haematopoietic and Lymphoid Tissues (19) was used to determine the precise type of leukemia or NHL.

Controls were selected at random from the roster of the study population in each country, matched on age and, in Russia, on region of residence at the time of the accident. The protocol called for 4 age-matched controls per case and for contacting potential controls until 4 controls were obtained for each case (thus refusing controls were replaced). In some instances, controls who accepted late were interviewed despite having been replaced. In Belarus, in addition, a small number of cases refused to participate or were found to be ineligible because their place of residence at the time of the accident was outside the two study regions. The controls which had given their consent and been interviewed for these cases were then post-hoc matched to the cases in order to increase the statistical power of the study. The controls had to be alive at the time of the diagnosis of the case to which they were matched. They were contacted by letter sent to their most recent address as registered in the Chernobyl Registries in Belarus and Russia, in the rosters of Chernobyl liquidators in Estonia, Latvia and Lithuania. Subjects no longer living at this address were traced through address bureaus, population registries, migration offices, Chernobyl liquidators' non-governmental organizations and local medical and social welfare institutions.

Information on personal behavior and work history of the liquidators in Chernobyl was collected through face-to-face interviews with the study subjects and/or a proxy (a relative or a colleague). The interviews were conducted by a trained interviewer with the use of a detailed standardized questionnaire which also included sections on demographic factors, on history of occupational and medical radiation exposures, of work with leukemogenic chemicals such as pesticides and organic solvents and on smoking and alcohol consumption.

Radiation dose estimation

Official data regarding individual doses received by liquidators are not available for all liquidators and are very uncertain (22). In the range of exposures received by the majority of liquidators, methods of biological dosimetry do not currently provide accurate and precise dose estimates for use in large-scale epidemiological studies, at least without prohibitive costs (23).

A multi-national group of dosimetrists and epidemiologists was set-up to develop and test methods for reconstruction of doses for subjects included in these studies. A method, entitled

RADRUE (Realistic Analytical Dose Reconstruction with Uncertainty Estimation), was developed (and extensively tested) to assess individual dose from external radiation received by the liquidators during their clean up missions.

The testing involved various intercomparisons exercises in which RADRUE doses were compared to the most reliable dose estimates available for different groups of liquidators (8). These included: professional workers from the Ministry of Atomic Energy who wore calibrated thermoluminescent dosimeters (TLD), as well as other liquidators with independent dose estimates based on unstable chromosome aberrations (dicentric) (24), and with independent dose estimates based upon Electron Paramagnetic Resonance (EPR) of tooth enamel (25). Correlations were generally good and served to improve and optimize the RADRUE process.

The method is described in detail elsewhere (26). The main idea of dose calculation by RADRUE is straightforward, based on calculation of external dose as a product of the exposure-rate and irradiation time, with shielding taken into account. The study questionnaire included detailed questions about (a) liquidator's routes to and from his work place(s) in the 30-km zone, (b) details about the work he performed, and (c) locations of residence and rest quarters used during his stay at Chernobyl. Dosimetry experts (AT, VG, AKM) familiar with the organization and conditions of work in the 30-km zone reviewed this information in detail and reconstructed the liquidators' type, location and duration of activities and itineraries. When the expert could not identify these with certainty, he entered two or more alternative itineraries and doses were calculated for each, with appropriate probabilities given to each. These itineraries were entered formally into the computer program for the RADRUE calculations and linked with data from an extensive database on exposure-rate measurements and interpolated values to calculate organ doses.

In some cases, because liquidators may have overestimated the amount of time they spent in specific high exposure-rate areas, results from the use of RADRUE were much higher than the permissible dose levels in force at the time of the work (from the end of May 1986, fairly efficient radiation protection practices were put in place to limit exposure of liquidators, except in exceptional circumstances, to 250 mGy in 1986 and 50 to 100 mGy in 1987, depending on the work). Therefore, a dose constraint procedure was introduced in RADRUE and doses were estimated with and without constraints. As these doses are thought to be more realistic, the main analyses in this paper are based on constrained doses; sensitivity analyses are also shown based on unconstrained doses.

Uncertainties (both shared and unshared) associated with the various aspects of the dose calculation are considered in RADRUE. Estimates of the uncertainties come from different sources. For example, a section of the RADRUE code calculates uncertainties associated with the exposure-rate interpolations for locations visited by the liquidator (shared). The expert estimates uncertainties for some of the variables, such as that associated with the speed of a vehicle when traveling a particular route. Uncertainties about information about the liquidator's work during the cleanup (unshared) and uncertainties associated with the parameter values (shared) are also included in RADRUE. Analysis of the uncertainties that are taken into account was implemented through stochastic modeling in RADRUE (26) and the output of the program was a set of 10,000 realizations of each of the study subject's dose. The main analyses below are based on the mean of these realizations.

For some liquidators, the RADRUE method could not be used because the level of detail about the time, place and type of work did not allow the experts to determine their likely itineraries. For these liquidators, a crude dose estimate based on the SEAD (Soft Expert Assessment Dosimetry) method (27) was provided. This involved classifying the liquidators according to the period in which they worked and the institution that sent them to the Chernobyl area and

assigning them an average dose based on independently documented working conditions and dosimetry control for these groups of workers. This average dose could be increased or decreased based on available questionnaire information for those study subjects on factors that may influence dose (e.g., time of beginning of clean-up activities and specific type of work in the Chernobyl area). Dose estimates obtained in this way are very uncertain. Subjects whose dose estimates were computed using the SEAD method were excluded from the main analyses.

In addition to the dose they received during their clean-up mission(s), liquidators who were residents of the South-Eastern part of Belarus could also receive non-negligible doses at their places of residence if they lived in highly contaminated areas and consumed locally produced milk or vegetables. Separate estimation of these doses and of their uncertainties was carried out using models previously developed for calculating average doses in contaminated settlements of Belarus (28–29). Such doses were not calculated for Russian and Baltic liquidators who were sent on mission from distant areas with low or no contamination.

For the purpose of the current study, the relevant target organ was taken to be the red bone marrow (RBM) and RBM doses were estimated in mGy.

Statistical methods

Basic descriptive analyses were conducted, including the distribution of cases and controls overall and by country, their age distribution as well as the distribution of other factors of interest, including characteristics of work as a liquidator, and known or potential risk factors or effect modifiers. Because of the small number of cases, they are presented for all hematological malignancies combined. Dose-response analyses were carried out for all hematological malignancies taken together, as well as for specific subtypes and groupings of subtypes of these diseases that are commonly studied in radiation epidemiology (all leukemia, leukemia excluding CLL, CLL, chronic myeloid leukemia (CML), acute leukemia and NHL) when the number of subjects was sufficient for this to be meaningful.

Data were analyzed by conditional logistic regression using the EPICURE software package (30). Two different risk models were fitted as follows. The primary risk model used was the linear ERR model, the model most commonly used in radiation epidemiology (31), where the estimate of the relative risk (RR), the odds ratio (OR), at a dose d , is expressed as $OR(d) = 1 + \beta d + \gamma d^2$, where β and γ denote, respectively, the slope coefficients of the linear and quadratic dose terms in the model. Analyses were also carried out with the model most generally used in occupational and environmental epidemiology (32), the log-linear risk model, in which the odds ratio at a dose d is expressed as $OR(d) = \exp(\beta d + \gamma d^2 + \dots)$. As can be seen below, within the range of doses in the data set, both risk models yielded very similar risk estimates. However, the ERR model is frequently unstable for the estimation of relatively small risks associated with relatively low doses, particularly when the number of subjects is small. Thus convergence problems are sometimes encountered in fitting this model, particularly with matched data or when interaction terms are included; the maximum likelihood estimate may not be finite or may be found on the boundary of the parameter space ($-1/\text{maximum dose}$) even in the case of a positive risk. Consequently, the log-linear risk model was used for the exploration of interactions, especially when looking at effect modification.

The main analyses included dose as a continuous variable and were carried out assuming a constant β . Departures from linearity of risk were explored by fitting polynomial equations in dose. Departures from a constant relative risk model were explored by carrying out analyses that address the possible modifying effects of other variables (including country, age at exposure, time since exposure, attained age) by the introduction of interaction terms between the factor considered and the radiation dose in the log-linear risk model. The statistical significance of model parameters was tested with the likelihood ratio test.

The effect of potential confounders (including education, occupation at the time of the Chernobyl accident, organization which sent the liquidator to Chernobyl and other known or suspected risk factors for which information was collected in the questionnaire) was tested by introducing them in the statistical analyses; a factor was taken to be a confounder of the association between radiation dose and the risk of hematological malignancy if it modified the OR by 10% or more.

Analyses were also conducted using dose as a categorical variable in six distinct categories (0-, 13.0-, 25.0-, 50.0-, 100.0- and 200.0 mGy) were carried out. The reference category includes all subjects whose dose was below the median of the dose distribution; the upper categories were chosen to span the width of this very skewed distribution. Estimated odds ratios and confidence intervals were calculated for the mean of each dose class.

As the main objective of radiation epidemiological studies is generally to test for an increased risk in relation to radiation exposure, one-sided *P* values and corresponding 90% confidence intervals are usually presented (31) and this is therefore the approach used here.

Effect of uncertainties in the dose estimates

A Monte Carlo Maximum Likelihood method (33–34) was used to take into account the dosimetric uncertainties in the risk estimates. This involved fitting the dose-response model to each of the 10,000 data sets corresponding to the 10,000 realizations of the doses for each subject. In each data set, a profile likelihood was determined by calculating the value of the likelihood at 100 fixed values of β , where β denotes the slope coefficient of the linear dose term in the model. These 100 values were chosen to cover the maximum likelihood estimate (β_{MLE}) and the range of possible confidence interval bounds. An integrated profile likelihood was then generated by averaging the likelihoods at each of the 100 points over all of the 10,000 simulations, thus providing a β_{MLE} and a confidence interval that take into account both the statistical error of the model and the dosimetric uncertainties. The maximum likelihood estimate (β_{MLE}) is taken to be the value of β for which the profile likelihood, $L(\beta)$, is at its maximum. Under appropriate regularity conditions, the difference between $-2 \ln[L(\beta)]$ and $-2 \ln[L(\beta_{MLE})]$ has an asymptotic (i.e. large sample) χ^2 distribution with one degree of freedom. The 90% confidence bounds were the values of β for which the χ^2 statistic is 2.7055.

Analytical strategy

Because of the large uncertainty in SEAD dose estimates and in the information about work in the Chernobyl area provided by family member proxies, the main analyses in this paper are restricted to liquidators whose dose was estimated with RADRUE and for whom the questionnaire was completed either by the liquidator himself or by a colleague (note that most SEAD estimates were in fact conducted for subjects for whom the questionnaire was completed by a family member). Sensitivity analyses were conducted to evaluate the robustness of the findings to these analytical choices.

Despite the requirement that the study population be restricted to subjects who had worked in the 30-km zone around the Chernobyl power plant, a number of subjects (largely from Belarus) had in fact never participated in the clean-up activities within the 30-km zone. This became evident only after interviews, as the Chernobyl Registry in Belarus (used to identify the study population) had no apparent indicator whether the liquidator worked in the 30- or 70 -km zone. Although these subjects were included in the main analyses, sensitivity analyses were conducted excluding these subjects.

The protocol called for verification of the specific case diagnoses by the international panel. However, for logistic reasons slides and case notes were not available for review for 27% of

cases and 15% of material submitted for review was judged to be inadequate for diagnosis. Because the proportion of cases for whom the original diagnosis was contradicted by the international panel was small (4%) when the material available was of sufficient quality, the main analyses include all of the cases, whether their diagnosis could be verified or not. Sensitivity analyses were also conducted excluding these subjects.

Results

Descriptive analyses

A total of 134 cases were originally ascertained; three cases were excluded by the international panel as their diagnosis was not eligible; and four cases (or family member proxies) could not be traced. Among the remainder, the participation rate was 92% overall (82% in Baltic countries, 87% in Russia, 97% in Belarus). Participation among controls was 73% in Baltic countries and 96% in Belarus. In Russia, where a detailed record of contacts made with eligible controls was not kept in all participating study regions, participation rates were estimated to be about 91%.

Overall, 117 eligible cases of neoplasms of lymphoid and hematopoietic tissue (69 leukemia, 34 NHL, eight multiple myeloma, two myelodysplasia and four cases of myeloproliferative disease, unclassifiable) were interviewed during the study period; the majority (69) were from Belarus, the rest (34 and 14 respectively) from Russia, and Baltic countries (Table 1). 481 controls were interviewed: 289, 136 and 56 from Belarus, Russia and Baltic countries, respectively.

A non-colleague proxy was interviewed for 47 cases; RADRUE doses could not be estimated for 12 of these cases and for five controls who were interviewed in person. Only 70 cases (58 who were interviewed in person and 12 with colleague proxies) and their 287 matched controls were included in the main analysis data set. Results below refer only to these study subjects.

The Belarusian study subjects differed substantially from the Russian and Baltic subjects: 81% were sent by civilian organizations (while the majority of Russian and Baltic liquidators were military reservists); 30% did not work in the 30-km zone (5% and 0%, respectively among Russians and Baltic liquidators); only 3.1% reported having worked on the industrial site of the Chernobyl power plant (63% and 53% respectively among Russians and Baltic liquidators). Twenty percent of the Lithuanian subjects reported having worked on the roof of the 3rd reactor and/or in other places close to the ventilation chimney (compared to 13% of Russians, 11% of Estonians and 0.4% of Belarusians). There were no major differences in reported type of activities between cases and controls.

The distribution of age at exposure was significantly different among the five countries ($P<0.001$) (Table 1). The Belarusian liquidators tended to be older at the moment of first exposure than their Russian counterparts or those of the Baltic countries: the median of ages at exposure were 43.6 in Belarus, 33.6 in Russia and 37.0 in Baltic countries (33.0 in Estonia). There was, however, no difference in age at exposure between cases and controls as they were matched on age at the time of the accident.

There was also a significant difference between subjects in Belarus and those in Russia and in Baltic countries with respect to the date of start of mission, with a higher proportion (63%) of Belarus liquidators having started work in the first two months after the accident (24% and 20% respectively in Russia and Baltic countries). Russian liquidators generally started work much later (median: November 1986) than their Belarus (median: June 1986) and Baltic (median: August 1986) counterparts. No difference in the distribution of date of start of mission between cases and controls was seen overall. Cases from Latvia and Lithuania tended to start

missions earlier than controls (respectively one and four months, not shown), but this difference was not statistically significant.

While none of the Baltic liquidators had more than one mission in the 30-km zone, 18% and 20% of Belarusian cases and controls and 6% of Russian cases and controls were sent on two missions or more. The median duration of mission among subjects with one mission only was shorter, however, in Belarus than elsewhere (33 days in Belarus, 57 in Russia, and 75 in Baltic countries), with 32% of subjects having had mission of less than one month (10% and 4% respectively among Russian and Baltic liquidators). No difference was observed in the duration of mission between cases and controls in Belarus and Russia; in Baltic countries, however, cases tended to have longer missions than controls (not shown).

Table 2 shows the distribution of a number of possible confounding factors among cases and controls by country. While there was little difference overall, controls in Baltic countries were more often married (92%) than cases (40%) and had a higher education level. Information about past medical radiation exposure was more often missing for cases than controls, mainly because of the number of deceased cases for whom proxies provided the information. Fewer cases reported ever having smoked (56%) than controls (66%); this difference was significant overall and in Belarus. Controls also reported alcohol consumption more often than cases; the difference was significant overall and in Baltic countries.

As indicated in methods above, the analyses shown in this paper, unless otherwise specified, are based on the mean of the dose realizations obtained from RADRUE. The distribution of mean RBM dose due to external exposure was very skewed (Figure 1): overall, 78% of RADRUE doses were below 50 mGy and only 14% were 100 mGy or more. On average, doses for liquidators from Belarus were much lower than for those from Russia and Baltic countries, even though they included doses received by liquidators in their places of residence in Belarus. Almost all liquidators from Belarus (95%) received doses below 50 mGy, compared to 41% and 55% respectively among Russian and Baltic liquidators. The median doses were 5.91 mGy (3.39 mGy if residential dose is excluded) in Belarus, 91.1 mGy in Russia and 43.5 mGy in Baltic countries.

The median doses tended to be higher among cases than controls overall (14.7 vs. 12.8 mGy), in Belarus (6.83 vs. 5.49 mGy), in Russia (105.9 vs. 82.9 mGy) and in the Baltic countries, where the difference was quite large (103.8 vs. 34.7 mGy), especially in Lithuania (177.4 vs. 61.5 mGy). Most of the study subjects received their doses at low dose-rates: only 7 subjects had dose-rates above 25 mGy/day and 11 between 10 and 25 mGy/day at some point during their mission.

Risk analyses

The ERR/100 mGy for all neoplasms combined was 0.60 (90% CI -0.02, 2.35) overall, of borderline statistical significance (Table 3), corresponding to a RR of 1.60 at 100 mGy; the ERR/100 mGy varied from 0.25 in Russia to 1.54 in Baltic countries, although this difference was not statistically significant; the corresponding estimates using the loglinear model were more consistent across countries (RR at 100 mGy 1.28 overall, ranging from 1.13 in Russia to 1.71 in Belarus). There was no evidence of departure from linearity (Figure 2). In analyses of OR by categorical levels of dose, the ORs were elevated in all categories compared to the reference, except in the 50–100 mGy category; the increase was statistically significant in the highest category (200+ mGy OR 3.71, 90% CI 1.20, 11.5). Excluding MM had little effect on the ERR/100 mGy (0.69, 90% CI 0.00, 2.71) or on the OR at 100 mGy based on the loglinear model (1.30, 90% CI 0.96, 1.76).

Risk estimates for specific subtypes and groupings of subtypes are also shown in Table 3. ERR/100 mGy for all leukemia excluding CLL was 0.50 (90% CI -0.38, 5.7) based on 19 cases and 83 controls; the corresponding estimate for NHL was 2.81 (90% CI 0.09, 24.3 – statistically significant, based on 20 cases and 80 controls). For CLL, the risk estimate was similar to the estimate for all leukemia combined – 0.47 (90% CI n.d., 7.6 and 0.48 (90% CI n.d., 3.3), respectively. Results of the log-linear analyses are slightly different, with ORs at 100 mGy of 1.42 (90% CI 0.49, 4.31) for leukemia excluding CLL and 1.41 (90% CI 0.82, 2.61) for NHL. In this analysis, the highest OR was seen for acute leukemia (8.31, 90% CI 1.17, 122, based on 6 cases and 25 controls) and it was statistically significantly elevated.

Results of sensitivity analyses

Table 4 shows the results of sensitivity analyses conducted to evaluate the robustness of the overall risk estimates to different analytic strategies. The results of log-linear analyses were generally similar to those reported above, although including subjects with proxy relative interviews reduced the OR at 100 mGy to 0.99. Analyses using unconstrained doses reduced the risk estimate to 1.07 (90% CI = 0.91, 1.23).

Results using the linear ERR model were more variable; restricting the analyses to subjects who worked in the 30-km zone yielded a statistically significantly elevated estimate (ERR/100mGy 0.66, 90% CI 0.00, 2.65).

Analyses restricted to cases who were matched with four controls yielded similar results, whatever the model used (not shown).

Attained age, age at exposure and time since exposure did not appear to modify the association between radiation dose and risk of hematological malignancies (not shown). Because of the small number of subjects with high dose-rate exposures, it was not possible to evaluate whether dose-rate modified the risk estimates.

None of the other factors studied (organization which sent the liquidators to Chernobyl, date of start of mission, duration of mission, work on industrial site, personal monitoring of dose, use of protective measures, education, marital status, occupational and medical history, smoking and alcohol consumption) appeared to play a role either as a confounder or a modifier of the association between radiation dose and risk (not shown).

Results of dose uncertainty analysis

The distribution of the 10,000 dose realizations for each subject was skewed and could be reasonably approximated by a log-normal. The geometric standard deviation for the subjects included in the main analyses varied from 1.15 to 3.98 with a mean of 1.85 and a standard deviation of 0.49.

Analyses adjusting for dosimetric uncertainties gave risk estimates that were very similar to the results derived from the standard analysis (Table 4) although the confidence intervals were, as would be expected, slightly wider. Figure 3 illustrates the integrated profile likelihood for the log-linear analyses: the resulting RR at 100 mGy was 1.29, 90% CI = 0.95 to 1.90 (Table 4). Figure 4 illustrates the integrated profile likelihood for the linear ERR analyses: the resulting ERR/100 mGy was 0.60, 90% CI = -0.01 to 2.58 (Table 4).

Discussion

This is one of the first studies of hematological malignancies in Chernobyl liquidators in which careful, individual dose reconstruction was attempted and in which information was sought on a number of potential risk factors. Overall, 70 cases and 287 controls from Belarus, Russia and

Baltic countries were included in these analyses. A significant increased risk was seen overall at doses of 200 mGy or above; the number of cases of leukemia and NHL were too small for meaningful analyses to be conducted within each more specific subtype of disease.

A number of issues must be considered in evaluating the results of this study.

Possible under-ascertainment of cases

Major efforts were made during the study, including verification of multiple sources, to identify all eligible cases. Belarus and the Baltic countries have long-running population based cancer registries, and this has facilitated verification of completeness of case ascertainment. This is not the case for Russia, where local cancer registries have been established more recently, after the accident, in the most contaminated areas and where it was not possible within the study to conduct a formal verification of the completeness of case ascertainment. While the number of cases observed in the Belarus and Baltic cohorts are similar or higher than expected, there appears to be some under ascertainment in Russia (observed to expected ratio: 0.79, based on age-specific incidence rates from Belarus cancer registry). It is conceivable that ascertainment of cases is less complete in Russia, particularly in some of the more remote regions included in this study.

It is difficult to evaluate precisely the possible impact of a potential under ascertainment. There is little reason to believe that, within a specific region, any under ascertainment would be related to dose level and hence it is unlikely that this would bias the results of the study, although it would, of course, reduce the statistical power. If liquidators from different regions had different potential for doses (as military reservists from the same region residence tended to be affected together) any under ascertainment related to region could be the source of a selection bias; as analyses were adjusted for the region of residence at the time of registration, any impact on risk estimates would be expected to be small. It is noted, however, that the risk estimates for the Russian liquidators were lower than those for Belarus and Baltic country liquidators.

Possibility of a selection bias due to survival

A total of 134 cases were originally ascertained in the study population of the five countries. Among these, 68 (51%) had died and proxy respondents were available for 57: of these seven were relatives together with colleagues (as was initially foreseen in the protocol), 43 - relatives only, five - colleagues only; for two cases information was extracted from records completed for compensation claims. The quality of information obtained from family member proxies concerning the conditions of work in the Chernobyl area was generally poor: there was much missing information and most of the proxies were rated by the interviewers as remembering poorly the details of the liquidator's history of work in Chernobyl. Interviews made with relatives were therefore excluded from the current analyses as their poorly defined exposures could bias risk estimates towards the null. In fact, analyses including cases for whom a proxy interview with a relative was obtained showed no increased risk in relation to radiation dose; this finding in fact reflects a significantly negative dose-response among subjects with proxy relatives.

It is possible, however, that exclusion of subjects who have died could induce a selection bias in this study, if survival was, for some reason, associated with exposure. Indeed, if cases who died had received higher doses, excluding them from the current analyses would lead to an underestimation of the relative risk of radiation-related hematological malignancies. We have little information to judge whether this has occurred. We have compared risk by period of diagnosis (before 1996 vs after since the proportion of cases who have died – and hence of proxy interviews – is higher (58%) in the earlier period than in the latter (41%)) and both risk estimates were comparable (not shown). Also, while the RR at 100 mGy was below one in

analyses restricted to all cases with a relative-proxy interview (RR at 100 mGy = 0.60, 90% CI 0.35, 0.94, based on 47 cases), it was significantly increased (RR at 100 mGy = 4.31, 90% CI 1.27, 22.5) when only relative-proxies judged by the interviewer to remember very well, well or fairly well the detailed conditions of the liquidator's work were included. This could be attributable either to a survival related selection bias (whereby cases who have died tended to have higher doses than those who survived and hence our risk estimates could be underestimated), or to a recall bias (with the proxy, knowing the subject has died, reporting conditions of work which would lead to higher doses, thus overestimating risk). Given the small number of cases (11) on which it is based, this result could also be due to chance.

Possibility of recall bias

Recall bias in the report of conditions of work as a liquidator might arise from the subjects' (or the proxies') awareness of their disease status.

It is difficult to precisely quantify the effects of different possible recall errors. Random errors, which are likely to have occurred given the difficulties of reporting accurately events, dates and working conditions occurring years in the past, will have induced an appreciable downward bias, if there is a true association between radiation dose and hematological malignancies. At the same time, however, if a differential recall bias exists between cases and controls, this could have produced a spurious positive association.

Differential recall bias could also have occurred, with cases attributing their disease to radiation and hence exaggerating their condition, place and duration of work. That smoking was underreported among cases compared to controls in most countries (Table 2), whether the liquidator himself or a proxy answered the questionnaire, suggests this. There was, however, no evidence of an association between the risk of hematological malignancies and possible individual determinants of radiation dose such as duration and place of work or type of activity (not shown). We think it is unlikely, therefore, that differential recall had a strong impact on the results of the present study.

Diagnostic verification

Although the study protocol called for verification of diagnosis by an international panel and despite the organization of a system for collection of histological material for diagnosis verification, it was not possible to gain access to the necessary material to review all of the diagnoses of cases included in the study. Results of the reviews of cases that have taken place are reassuring, however; when material and/or sufficiently detailed abstracts from medical records were available (73% of cases), the percent of diagnostic agreement was quite high (as was observed in a similar study in Ukraine (35)): all but three diagnoses were classified as myeloid or lymphoid malignancies eligible for the study. Within each category, determination of more precise type of malignancy was not always achievable, however, either due to the poor technical quality of the slides or because the abstracts from medical records were not sufficiently informative. As a result, two cases of leukemia were classified as of unspecified cell type and six cases of myeloid malignancies - as myelodysplastic/myeloproliferative diseases, unclassifiable.

Although not all cases could be reviewed formally, it is unlikely that the results of the study would be materially changed if they had been. Indeed, although the ERR estimates are reduced, the RR estimates based on the log-linear model are virtually unchanged when analyses are restricted to cases with verified diagnosis and their matched controls.

Statistical power of the study

Power calculations were performed at the outset of this study, using information on the distribution of dose in the study population from results of a previous pilot study (36), in which it was found that 50% of the subjects had registered doses of 100 mGy or more, and estimates of radiation induced risk of leukemia among adult atomic bomb survivors in the first 10 years following exposure. With the assumption of a linear relation between exposure level and the excess relative risk, it was felt that the study had sufficient power (80%) at the 0.05 critical level and in a one-sided framework, to find an increased RR of the order of 3 at 250 mGy if it existed.

The reconstructed doses – particularly in Belarus – were lower than those found in the pilot study, but the power of our study based on the reconstructed doses remains very similar. However, there were large uncertainties in dose (23–26), thus reducing the real statistical power of the study. The inadequacy of the information obtained from proxies for deceased subjects also greatly reduced the number of subjects that were available for analysis and hence the number of cases was too small for meaningful analyses to be conducted of specific types and subtypes of hematological malignancies. As the current study was underpowered, the non-significant dose-response relationships need to be interpreted with caution.

A similar study of hematological malignancies and pre-cancerous lesions was recently completed in Ukraine (8), with a similar protocol and the same dose reconstruction approach. Future combined analyses are envisaged in order to maximize the information about radiation risks that can be drawn from this important population.

Possible selection bias related to exclusion of cases in first years after the accident

A relatively short latency is generally assumed for radiation-induced leukemia compared to most solid tumors as increased risks have been observed within a few years of exposure. In the present study, case ascertainment for the largest cohorts (Belarus and Russia) only begun in 1993, approximately six to seven years after the bulk of the exposure to radiation from the Chernobyl accident, and employment of workers as liquidators. This restriction was due to the likely inadequate cancer registration in these countries in the first years after the accident.

Although the risk of radiation-induced leukemia in other populations is known to decrease with time since exposure, the annual decrease appears in fact to be small for subjects who were exposed as adults (2). It is unlikely, therefore, that the relative risk estimates for Belarusian and Russian liquidators would be substantially biased by the failure to include earlier cases.

In the Baltic countries, where case ascertainment begins in 1990 and therefore covers a period more proximate in time to the accident, the risk estimates might encompass some or all of the prompt effect of radiation exposure. In fact, the ERR/100 mGy for Baltic liquidators, based on 10 cases and 39 controls, was 1.54 (90% CI –0.04, 33.9), much higher than those in Russia (ERR/100 mGy 0.25) and in Belarus (ERR/100 mGy 0.64), although this difference was not statistically significant (Table 3). However, the corresponding estimates using the loglinear model were more consistent across countries, the RR at 100 mGy was higher in Baltic countries (1.42) than in Russia (1.13) but lower than in Belarus (1.71) (Table 3).

Systematic and random errors in dose estimates

The reconstructed doses in Belarus were particularly low compared to other countries (Figure 1), although the majority of these liquidators had started work within two months of the accident. This difference is similar when the average official doses recorded in national registries are compared (37) and appears to reflect the very low percentage of Belarusian liquidators who reported having worked on the industrial site of the Chernobyl power plant.

In addition, most of the Belarusian subjects were civilians whereas most of the Russian and Baltic liquidators were military reservists: the types of work they conducted were therefore different, as was their exposure potential (26).

We have, however, investigated the possibility that a systematic difference in the adequacy of reconstructed doses across countries could be responsible for the different dose distribution in Belarus and elsewhere. During the interview, information about doses was also obtained from official documents that some of the liquidators had received. Official doses were thus available for 92 out of the 598 liquidators included in the current study (16 from Belarus, 46 from Russia, 5 from Estonia, 1 from Latvia and 24 from Lithuania). The correlation between official doses and doses estimated with RADRUE was reasonable (correlation coefficient = 0.42). RADRUE doses appeared to be substantially lower than official doses, however, among Belarus military reservists (the only category of liquidators that was sufficiently represented in all countries) compared to their Russian and Lithuanian counterparts, thus, supporting a possible systematic difference across countries. This result is based on only 8 subjects in Belarus, however, and re-examination of the reported Chernobyl related work history of these liquidators does not indicate any obvious underestimation of doses. As only 13% of the Belarus liquidators were military reservists, and as official doses are known to be uncertain and of variable reliability depending on the sources, we have little objective information to conclude about a possible systematic difference in dose-reconstruction between countries, particularly since the dose-reconstruction process was subject to substantial checking and intercomparisons.

Major efforts were made in this study to evaluate individual radiation doses – to develop, test, optimize and implement a robust method of dose estimation. The accuracy and precision of individual estimates depends, nevertheless, on the quality of the completed questionnaires and is related to the type of work the liquidator performed. Professional radiation workers, for example, generally had a much more precise recollection of the work they carried out and of its location and timing than did military reservists who may have traveled all over the 30-km zone performing similar work in areas with varying radiation levels. Uncertainties depend also on the completeness of input dosimetric data and the adequacy of the assumptions made to extrapolate such data for periods and places where direct measurements were lacking. Efforts were made to characterize these uncertainties (26) and the dose-reconstruction yielded a set of realizations of doses for each subject that reflected these uncertainties. Analyses that make full use of these realizations were conducted, with a Monte Carlo Maximum Likelihood approach, and yielded similar risk estimates and confidence intervals that were only very slightly wider than those derived from the standard analyses.

As blood samples from the study subjects have been collected and stored, a reassessment of doses and of the risk estimates may be possible in the future, should sufficiently sensitive and specific biological markers of low doses become available.

Possible bias resulting from confounding

Information was collected by questionnaire on a number of different risk factors for leukemia and cancer in general. These included socio-economic status (measured by education and by occupation at the time of the Chernobyl accident), other sources of radiation exposure (medical and occupational), occupational exposure to a number of workplace carcinogens, as well as smoking and alcohol consumption. Adjustment for these factors in the estimation of risk of hematological malignancies did not, however, materially affect the risk estimates; these factors are therefore unlikely to be strong confounding factors for these diseases.

Attained age, age at exposure and time since exposure also did not appear to have an impact on the risk estimates as modifiers.

Consistency with previously published findings

A primary objective of the study presented here was the estimation of risk of hematological malignancies following protracted exposures leading to low to moderate doses. Table 5 shows a comparison of the risk estimates in this study with those derived from analyses of male adult atomic bomb survivors, as well as from two recent low dose studies, the 15-country nuclear industry study and the study of the Techa River cohort.

The estimate of ERR/100 mGy for leukemia excluding CLL is higher but statistically compatible with those based on the atomic bomb survivors and the 15-country study. They are of the same order of those seen in the Techa River cohort (7).

The central estimate of ERR/100 mGy for NHL is, however, much higher than those based on previous studies. This estimate is very uncertain however and is statistically compatible with other estimates. It should be noted that NHL cases were included in the present study because the distinction between lymphoid leukemia and lymphoma can be artificial. Because of insufficient material and changes in classification schemes since 1990, it was not possible to review these cases in sufficient detail and a substantial proportion of these lymphomas might actually be considered as leukemia using the WHO classification of Tumours of Haematopoietic and Lymphoid Tissues (19). This is the reason leukemia and lymphoma have been combined in most of the analyses in the current paper; again, the combined estimate is slightly higher than, but compatible with, comparable estimates from other studies of populations with low dose exposures.

In a view of the lack of solid evidence for a positive relationship between CLL and radiation, the observed increase in the risk of CLL may be surprising. However, along with better understanding of the pathobiology of CLL, our findings are consistent with the latest discussions on necessity to further elucidate the association between CLL and ionizing radiation (38–40).

Conclusion

The current paper presents the results of a multinational case-control study of risk of hematological malignancies among Chernobyl liquidators in which considerable efforts were made to reconstruct and validate individual dose estimates. A significantly elevated OR was seen for all hematological malignancies combined at doses of 200 mGy and above. Although most risk estimates are not statistically significantly elevated, they are based on small numbers of cases and they are statistically compatible with those obtained for atomic bomb survivors and recent low dose-rate studies. Although sensitivity analyses showed generally similar results, we cannot rule out the possibility that biases and uncertainties could have led to over or underestimation of the risk in this study. This study adds to the body of evidence on the effects of low dose-rate exposures to ionizing radiation.

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Figure 1. Distribution of total RBM dose¹ among study subjects (overall, by country, and by case-control status) (results based on the main data set²)

¹The doses are based on the mean of the realizations calculated with the uncertainties program in RADRUE

²Liquidators whose dose was estimated with RADRUE and with interview data with liquidators or colleagues

Figure 2.

³ Comparison of odds ratios (ORs) predicted by different risk models with categorical odds ratios estimated in 6 dose categories (results based on the main data set ⁴)

◆ OR and 95% CI

— Log-linear model – linear dose-response

- - - Log-linear model – linear-quadratic dose-response

— ERR model – linear dose-response

- - - x - - - ERR model – linear-quadratic dose-response

³The doses are based on the mean of the realizations calculated with the uncertainties program in RADRUE

⁴Liquidators whose dose was estimated with RADRUE and with interview data with liquidators or colleagues

Figure 3. Profile likelihood, MLE and 90% CI for β from both the unsimulated data and the 10,000 simulations, using the log-linear model - All hematological malignancies combined (*results based on the main data set*⁵)

⁵Liquidators whose dose was estimated with RADRUE and with interview data with liquidators or colleagues

Figure 4. Profile likelihood, MLE and 90% CI for β from both the unsimulated data and the 10,000 simulations, using the linear ERR model - All hematological malignancies combined (*results based on the main data set*⁶)

⁶Liquidators whose dose was estimated with RADRUE and with interview data with liquidators or colleagues

Table 1

Distribution of study subjects by country - All hematological malignancies combined (*results based on the main data set* ⁷)

	Total	Belarus	Russia	Baltic countries
All liquidators				
Number of cases				
All malignancies	117	69	34	14
Leukemia only	69	43	18	8
Acute lymphoid leukemia	4	3	0	1
Acute Myeloid Leukemia	11	4	5	2
Chronic lymphoid leukemia	32	20	8	4
Chronic myeloid leukemia	11	8	3	0
Other	11	8	2	1
Non-Hodgkin's lymphoma	34	17	13	4
Other malignancies ⁸	14	9	3	2
Number of controls	481	289	136	56
Main data set ^a				
Number of cases				
All malignancies	70	44	16	10
Leukemia only	40	27	8	5
Acute lymphoid leukemia	2	2	0	0
Acute myeloid leukemia	4	1	1	2
Chronic lymphoid leukemia	21	13	5	3
Chronic myeloid leukemia	7	6	1	0
Other	6	5	1	0
Non-Hodgkin's lymphoma	20	11	6	3
Other malignancies	10	6	2	2
Number of controls	287	185	63	39
Number of subjects				
Did the subject work in the 30 km zone?				
Yes (inside)	285	161	75	49
No (outside)	72	68	4	0
P-homogeneity between countries	< 0.001			
By age at exposure				
Median	39.8	43.6	33.6	37
Range	19–60	21–60	19–49	27–51
< 35	144	81	43	20
35–49	163	100	36	27

⁷Liquidators whose dose was estimated with RADRUE and with interview data with liquidators or colleagues

⁸Myelodysplasia, myeloproliferative disease and, in Belarus, multiple myeloma

	Total	Belarus	Russia	Baltic countries
50+	50	48	0	2
<i>P-homogeneity between countries</i>	<i>< 0.001</i>			
By date of beginning of mission				
Median	03/07/1986	05/06/1986	20/11/1986	08/08/1986
Range	26/04/1986-18/12/1987	26/04/1986-23/11/1987	29/04/1986-18/12/1987	26/04/1986-17/11/1987
< 15 May 1986	104	87	10	7
15 May-30 June 1986	69	57	9	3
1 July-31 August 1986	52	26	10	16
1 September-31 December 1986	61	38	16	7
1 January-31 December 1987	71	21	34	16
<i>P-homogeneity between countries</i>	<i>< 0.001</i>			
By duration of mission (days) ⁹				
Median	54	33	57	75
Range	2-615	2-615	12-337	18-221
<16	38	36	2	0
16-30	27	20	5	2
31-60	101	57	32	12
61-149	97	40	29	28
150+	34	23	5	6
<i>P-homogeneity between countries</i>	<i>< 0.001</i>			

^aLiquidators whose dose was estimated with RADRUE and with interview data with liquidators or colleagues

⁹Subjects with one mission only

Distribution by potentially confounding factors, by case-control status – All hematological malignancies combined (results based on the main data set)^a

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Table 2

	Total		Belarus		Russia		Baltic countries	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Family status								
Married	62	262	43	171	15	55	4	36
Single	2	5	0	1	0	3	2	1
Widowed	1	6	1	5	0	1	0	0
Divorced	3	13	0	7	1	4	2	2
Missing	2	1	0	1	0	0	2	0
<i>P</i> -homogeneity	0.28		0.71		1.00		0.001	
Education level								
Eight class or less	16	52	9	32	3	7	4	13
High school	24	99	14	71	5	19	5	9
Special high school	12	66	7	36	5	19	0	11
Higher school	17	68	14	46	3	16	0	6
Missing	1	2	0	0	0	2	1	0
<i>P</i> -homogeneity	0.64		0.68		0.90		0.04	
Past occupational exposure to radiation								
Yes	6	29	3	15	3	10	0	4
No	61	255	41	170	11	51	9	34
Missing	3	3	0	0	2	2	1	1
<i>P</i> -homogeneity	0.18		1.00		0.24		0.35	
Exposure to occupational carcinogens								
Yes	6	22	3	8	0	5	3	9
No	62	250	41	176	15	49	6	25
Missing	2	15	0	1	1	9	1	5
<i>P</i> -homogeneity	0.75		0.55		0.56		0.87	
Exposure to organic solvents								
Yes	1	3	1	1	0	0	0	2

^aLiquidators whose dose was estimated with RADRUE and with interview data with liquidators or colleagues

	Total		Belarus		Russia		Baltic countries	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
No	67	274	43	183	15	55	9	36
Missing	2	10	0	1	1	8	1	1
<i>P-homogeneity</i>	0.88		0.47		0.68		0.61	
Exposure to pesticides								
Yes	3	2	2	1	0	0	1	1
No	65	275	42	183	15	55	8	37
Missing	2	10	0	1	1	8	1	1
<i>P-homogeneity</i>	0.08		0.17		0.68		0.18	
Past medical radiation exposure								
Yes	57	232	37	149	13	46	7	37
No	8	51	6	35	2	14	0	2
Missing	5	4	1	1	1	3	3	0
<i>P-homogeneity</i>	0.02		0.28		0.59		0.01	
Smoking status at the time of the diagnosis^b								
Current	27	163	11	92	12	43	4	28
Past	12	28	9	21	2	5	1	2
Non smoker	29	96	24	72	1	15	4	9
Missing	2	0	0	0	1	0	1	0
<i>P-homogeneity</i>	0.003		0.01		0.11		0.09	
Alcohol consumption status at the time of the interview								
Yes	56	245	36	157	13	52	7	36
No	11	42	8	28	2	11	1	3
Missing	3	0	0	0	1	0	2	0
<i>P-homogeneity</i>	0.01		0.65		0.30		0.04	

^aLiquidators whose dose was estimated with RADRUE and with interview data with liquidators or colleagues

Risk estimates based on the linear ERR and log-linear models, overall, by country and by disease type and subtype (results based on the main data set)^a

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Table 3

	Cases/Controls	Linear ERR model			Log-linear model		
		ERR/100 mGy	90% CI	RR at 100 mGy	RR at 100 mGy	90% CI	90% CI
<i>All hematological malignancies combined</i>							
Overall	70/287	0.60	−0.02 2.35	1.60	1.28	0.95 1.74	
<i>Country-specific</i>							
Belarus	44/185	0.64	−0.57 4.44	1.64	1.71	0.42 6.05	
Russia	16/63	0.25	nd ^b 2.83	1.25	1.13	0.72 1.76	
Baltic Countries	10/39	1.54	−0.04 33.9	2.54	1.42	0.91 2.26	
<i>P-homogeneity between countries</i>		0.75			0.78		
<i>Leukemia</i>							
All	40/165	0.48	nd ^b 3.31	1.48	1.20	0.76 1.87	
All, excluding chronic lymphoid leukemia	19/83	0.50	−0.38 5.70	1.50	1.42	0.49 4.31	
Chronic lymphoid leukemia	21/82	0.47	nd ^b 7.61	1.47	1.16	0.68 1.89	
Chronic myeloid leukemia	7/34	198.7	nd ^b nd ^b	199.7	2.77	0.52 22.3	
Acute	6/25	6.27	−0.11 nd ^b	7.27	8.31	1.17 121.6	
<i>NHL</i>							
	20/80	2.81	0.09 24.3	3.81	1.41	0.82 2.61	

^aLiquidators whose dose was estimated with RADRUE and with interview data with liquidators or colleagues

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bNot defined
bNot defined
bNot defined
bNot defined
bNot defined
bNot defined

Risk estimates based on the linear ERR and log-linear models – impact of different analytic strategies - All studied hematological malignancies combined
(results based on the main data set ^a)

	Cases/Controls	Linear ERR model			Log-linear model		
		ERR/100 mGy	90% CI	RR at 100 mGy	RR at 100 mGy	90% CI	90% CI
Different populations							
Subjects who worked in 30 km zone	54/180	0.66	0.00 2.65	1.66	1.29	0.95 1.77	
Cases with confirmed diagnosis and their matched controls	34/140	0.28	-0.24 2.34	1.28	1.26	0.69 2.35	
Cases with confirmed diagnosis and their matched controls (30 km zone)	27/83	0.29	-0.24 2.41	1.29	1.28	0.69 2.49	
Entire population ^b	117/481	0.00	nd c	0.99	0.99	0.77 1.26	
Entire population excluding SEAD doses ^d	105/429	0.25	-0.10 1.13	1.25	1.15	0.87 1.50	
Dose without constraint	70/287	0.14	-0.06 0.89	1.14	1.07	0.91 1.23	
Unconditional logistic regression ^e	70/429	0.39	-0.06 1.57	1.39	1.24	0.92 1.65	
Dose uncertainties	70/287	0.60	-0.01 2.58	1.60	1.29	0.95 1.90	

^aLiquidators whose dose was estimated with RADRUE and with interview data with liquidators or colleagues

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^bAll liquidators included in the case-control study: their dose was estimated by the RADRUE method or by the SEAD method, and their interview data was completed by

^cNot defined

^dAll liquidators included in the case-control study except those whose dose was estimated by the SEAD method

^eStratified on region and age at the time of the accident in 9 categories (<25, 25–30, 30–35, 35–40, 40–45, 45–50, 50–55, 55–60 and 60+)

Comparison of risk estimates (and 90% confidence intervals) with comparable estimates from the atomic bomb survivors, nuclear workers and Techa River cohort studies – Leukemia excluding CLL

Table 5

	Number of ERR/100		RR at 100		90% CI	
	cases	mSv		mSv		90% CI
Atomic bomb survivors ¹⁹						
Linear dose-response	83	0.32	0.18	0.52	1.32	
Linear-quadratic dose-response	83	0.15 20	-0.08	0.46	1.15 ^b	
15-country nuclear workers						
study	196	0.19	<0.21	0.71	1.19	
Techa River cohort						
Chernobyl liquidators	60	0.46	0.17	1.23	1.46	
Leukemia excluding CLL						
Linear ERR model	19	0.50	-0.38	5.70	1.50	
Log-linear model	19				1.42	0.49 4.31
All hematological malignancies						
Linear ERR model	70	0.60	-0.02	2.35	1.60	
Log-linear model	70				1.28	0.95 1.74

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¹⁹Analyses carried out at IARC – Men exposed between ages of 20 and 60

²⁰Linear term of linear-quadratic ERR model with modification by sex, age at exposure and time since exposure

²¹ <0 : Lower confidence bound is on boundary of parameter space ($-1/\text{maxdose}$)