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## The Ukrainian-American Study of Leukemia and Related Disorders Among Chernobyl Cleanup Workers from Ukraine: I. STUDY METHODS

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### Abstract

Thus far there are relatively few data on the risk of leukemia among those who were exposed to external radiation during cleanup operations following the Chernobyl nuclear accident, and results have not been consistent. To investigate this issue 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 were estimated using a new time-and-motion method known as RADRUE (Realistic Analytical Dose Reconstruction with Uncertainty Estimate). See companion paper II for a detailed description of the dosimetry. 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.

The dose-response analysis and results are given in companion paper III.

### INTRODUCTION

Following the accident at the Chernobyl (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 two weeks, the cleanup workers were exposed primarily to external irradiation from gamma-emitting radionuclides, with those workers sent earliest receiving the highest doses. Estimates derived

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from national Chernobyl 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). 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, the corresponding estimates are 169 mGy, 92 mGy and 34 mGy; for Belarus, 60 mGy, 28 mGy and 20 mGy.

Studies of cancer among cleanup workers have so far 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 methodologic limitations but seem to point to a possible raised risk of leukemia in this population. Until recently, most of the epidemiologic research has been based on national Chernobyl registries, particularly the National Medical and Dosimetric Registry in Russia – for example (4,5). The strongest of the registry-based studies from a methodologic 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 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.

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 Chernobyl 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 methodologically more rigorous studies that have been reported are also based on 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 Gray 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.

The more recent registry study (8) was based on a cohort of 162,684 Russian cleanup workers. After allowing for a two-year latency period, 41 leukemia cases were diagnosed between 1986–1995, of which 13 were CLL. The estimated ERR per Gray was 1.33 (95% CI: –6.3, 8.9) for all leukemia, and 15.59 (95% CI: –24.9, 56.1) for leukemia excluding CLL. Again, however, an analysis of the earliest workers on site who appeared to receive the highest doses produced smaller ERRs, so there was again 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. Moreover, the first study included a comparison with national leukemia incidence rates.

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, more than the case totals of earlier studies. The increased statistical power leads to a more precise evaluation of the possible increased risk of leukemia among Chernobyl 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, respectively, 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 following the Chernobyl 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. 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 two-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 (female cleanup workers being considered too few 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 study was carried out in a four-year period, 2001–2004, and was focused on the identification and validation of cases of leukemia that occurred between 1986 and 2000, together with matched controls. 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 upon 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 Chernobyl accident in order to reveal health effects and

make decisions about the provision of medical care and social security. The Registry covers over 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 Chernobyl (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, through intensive search of local medical institutions, 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 not liquidators and 27 had been miscoded so that 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 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, U.K.; 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 biologic 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 four-five 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. Following the examination of every five cases, each expert expressed his or her opinion regarding diagnosis, 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, eleven negative controls were randomly included 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 Griep 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. Following 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 (2 ineligible, 7 not traced, 4 refusals, 3 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 randomly selected 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. In order to be certain of identifying five appropriate controls, a list of nine controls were compiled for each case. 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.

## Tracing and Recruitment

For both cases and controls, current addresses (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 Chernobyl 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 which issues certificates to victims of the Chernobyl 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 only be used on 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 Chernobyl 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.A. 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 co-worker if the subject is deceased, is combined with data on the radiation dose rates at the locations and dates where the liquidator spent any time in order to reconstruct a history of doses received during the time the liquidator was involved in cleanup activities.

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 Chernobyl reactor in order 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 allows 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.

In order 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 co-workers 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 co-worker 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.

Co-worker proxies were identified either by next-of-kin or employment records for the index subject. To locate co-worker 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 Chernobyl, 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-Chernobyl 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 Chernobyl 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 which 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 (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: Risk = background risk  $\times$  (1.0 + excess relative risk (ERR)  $\times$  dose  $\times$  exp [ $\sum_i y_i Z_i$ ]), (Equation 1), where  $Z_i$  represents potential modifying factors with their corresponding parameters  $y_i$ . The absorbed doses to bone marrow, lagged by two 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 Gray (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 upon the category (i.e., subject, next-of-kin, co-worker). 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 eight additional leukemias were identified. 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 two-thirds 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 casecontrol designs in which there is potential for biased recall of events.

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 biologic 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 Chernobyl 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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## References

1. Hatch M, Ron E, Bouville A, Zablotska L, Howe G. The Chernobyl disaster: cancer following the accident at the Chernobyl nuclear power plant. *Epidemiol. Rev* 2005;27:56–66. [PubMed: 15958427]
2. Bouville A, Chumak VV, Inskip PD, Kryuchkov V, Luckyanov N. The Chornobyl accident: Estimation of radiation doses received by the Baltic and Ukrainian cleanup workers. *Radiat. Res* 2006;166:158–167. [PubMed: 16808604]
3. NRC National Research Council. Health effects of exposure to low levels of ionizing radiation (BEIR V). Washington DC: National Academy Press; 1990.
4. Ivanov VK, Tsyb AF, Gorsky AI, Maksyutov MA, Rastopchin EM, Konogorov AP, Korelo AM, Biryukov AP, Matyash VA. Leukaemia and thyroid cancer in emergency workers of the Chernobyl accident: Estimation of radiation risks (1986–1995). *Radiat. Environ. Biophys* 1997;36:9–16. [PubMed: 9128893]
5. Ivanov VK, Tsyb AF, Gorsky AI, Maksyutov M, Khait SE, Preston DL, Shibata Y. Elevated leukemia rates in Chernobyl accident liquidators. *BMJ, Rapid Responses*. 2003
6. Buzunov, VN.; Omelyanets, N.; Strapko, NP.; Ledoschuk, B.; Krasnikova, LI.; Kartushin, GI. Chernobyl NPP accident consequences cleaning up participants in Ukraine health status epidemiologic study main results. In: Karaoglou, A.; Desmet, G.; Kelly, GN.; Menzel, HG., editors. *The Radiological Consequences of the Chernobyl Accident; Proceedings of the First International Conference; Minsk, Belarus: European Commission; 1996. p. 871-878.*
7. Ivanov VK, Tsyb AF, Konogorov AP, Radtopchin EM, Khait SE. Case-control analysis of leukemia among Chernobyl accident emergency workers residing in the Russian Federation, 1986–1993. *J. Radiol. Prot* 1997;17:137–157.
8. Konogorov AP, Ivanov VK, Chekin SY, Khait SE. A case-control analysis of leukemia in accident emergency workers of Chernobyl. *J. Environ. Pathol. Toxicol. Oncol* 2000;19:143–151. [PubMed: 10905520]
9. Chumak VV, Voilleque P, Bakhanova E, Golovanov I, Luckyanov N, Sholom S, Kryuchkov V, Bouville A. The Ukrainian-American Study Of Leukemia And Related Disorders Among Cleanup Workers From Ukraine: II. ESTIMATION OF BONE-MARROW DOSES. *Rad Res* (submitted). 2008
10. Romanenko, AY.; Finch, S.; Hatch, M.; Lubin, J.; Bebesko, VG.; Bazyka, DA.; Gudzenko, N.; Dyagil, IS.; Reiss, R.; Bouville, A.; Chumak, VV.; Trotsiuk, NK.; Babkina, NG.; Belayev, Y.; Masnyk, I.; Ron, E.; Howe, GR.; Zablotska, LB. The Ukrainian-American Study Of Leukemia And Related Disorders Among Cleanup Workers From Ukraine: III. RADIATION RISKS. *Rad Res* (submitted). 2008
11. Cardis E, Gilbert ES, Carpenter L, Howe G, Kato I, Armstrong BK, Beral V, Cowper G, Douglas A. Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. *Radiat. Res* 1995;142:117–132. [PubMed: 7724726]
12. Finch SC. Myelodysplasia and radiation. *Radiat. Res* 2004;161:603–606. [PubMed: 15161362]
13. Heaney ML, Golde DW. Myelodysplasia. *N. Engl. J. Med* 1999;340:1649–1660. [PubMed: 10341278]
14. Romanenko, A.; Beebe, G.; Bebesko, V.; Howe, G.; Thomas, T.; Ledoschuk, B.; Kortushin, G.; Gudzenko, N.; Burch, J.; Chumak, V.; Bouville, A.; Masnyk, I.; Timarche, M. Leukemia: Results of a two year feasibility study. In: Voizianov, A.; Bebesko, V.; Bazyka, D., editors. *Health effects of Chornobyl accident: Monograph in 4 parts. Kyiv: DIA Ltd; 2003. p. 38-53.*
15. Howe GR. Use of computerized record linkage in cohort studies. *Epidemiol. Rev* 1998;20:112–121. [PubMed: 9762514]

16. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, Sultan C. Proposals for the classification of the acute leukaemias. French-American-British (FAB) co-operative group. *Br. J. Haematol* 1976;33:451–458. [PubMed: 188440]
17. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, Sultan C. Proposed revised criteria for the classification of acute myeloid leukemia. A report of the French-American-British Cooperative Group. *Annals of internal medicine* 1985;103:620–625. [PubMed: 3862359]
18. Jaffe, E.; Harris, N.; Stein, H.; Vardiman, J., editors. IARC. World Health Organization Classification of Tumours, Pathology and Genetics of Tumors of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2001.
19. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Blade J, Boccadoro M, Child JA, Avet-Loiseau H. International staging system for multiple myeloma. *J. Clin. Oncol* 2005;23:3412–3420. [PubMed: 15809451]
20. Preston DL, Kusumi S, Tomonaga M, Izumi S, Ron E, Kuramoto A, Kamada N, Dohy H, Matsuo T. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950–1987. *Radiat. Res* 1994;137:S68–S97. [PubMed: 8127953]
21. Preston, DL.; Lubin, JH.; Pierce, DA.; McConney, ME. EPICURE User's Guide. Seattle, WA: Hirosoft International Corporation; 1993.
22. Dyagil I, Adam M, Beebe GW, Burch JD, Gaidukova SN, Gluzman D, Gudzenko N, Klimenko V, Peterson L, Reiss R, Finch S. Histologic verification of leukemia, myelodysplasia, and multiple myeloma diagnoses in patients in Ukraine, 1987–1998. *Int. J. Hematol* 2002;76:55–60. [PubMed: 12138896]

**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	%	N	%
<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	100,0	110645	100,0

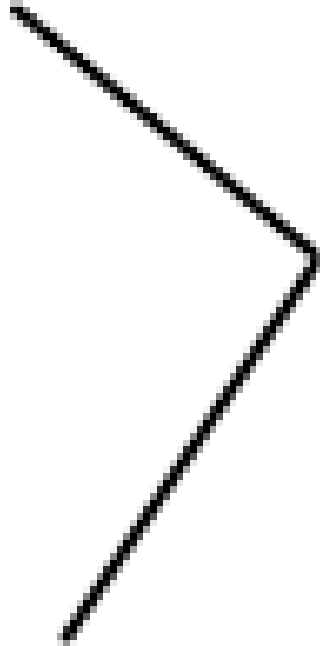
**Table 2**

Distribution of the Cohort members by oblast of residence at the time of registration in the SRU.

Oblast	Year of clean up				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	<b>70894</b>	<b>16474</b>	<b>14707</b>	<b>8570</b>	<b>110645</b>

**Table 3**

Distribution of Confirmed Cases by Type

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

<sup>a</sup> 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

**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