Childhood leukaemia in Belarus, Russia, and Ukraine following the Chernobyl power station accident: results from an international collaborative population-based case–control study

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Background There is little evidence regarding the risk of leukaemia in children following exposure to radionuclides from the Chernobyl Nuclear Power Plant explosion on April 26, 1986.

Methods This population-based case–control study investigated whether acute leukaemia is increased among children who were in utero or <6 years of age at the time of the Chernobyl accident. Confirmed cases of leukaemia diagnosed from April 26, 1986 through December 31, 2000 in contaminated regions of Belarus, Russia, and Ukraine were included. Two controls were matched to each case on sex, birth year, and residence. Accumulated absorbed radiation dose to the bone marrow was estimated for each subject.

Results Median estimated radiation doses of participants were <10 mGy. A significant increase in leukaemia risk with increasing radiation dose to the bone marrow was found. This association was most evident in Ukraine, apparent (but not statistically significant) in Belarus, and not found in Russia.

Conclusion Taken at face value, these findings suggest that prolonged exposure to very low radiation doses may increase leukaemia risk as much as or even more than acute exposure. However the large and statistically significant dose–response might be accounted for, at least in part, by an overestimate of risk in Ukraine. Therefore, we conclude this study provides no convincing evidence of an increased risk of childhood leukaemia as a result of exposure to Chernobyl radiation, since it is unclear whether the results are due to a true radiation-related excess, a

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Introduction

The explosion of Reactor Number 4 at the Chernobyl Nuclear Power Station on April 26, 1986 resulted in the largest accidental release of radionuclides into the environment in history. The radioactive plume contaminated large areas, and prevailing winds spread short-lived (primarily noble gases and radiiodines) and medium and long-lived (including $^{137}$Cs and $^{134}$Cs) radionuclides over portions of Ukraine, Belarus, Russia, areas of Europe, Scandinavia, and western Asia. The wide geographic dispersion of radionuclides, the large number of individuals potentially exposed, and concerns over the known leukemogenic effect of ionizing radiation prompted the initiation of a number of epidemiological studies to investigate the relationship of Chernobyl-related radiation exposure and leukemia risk.

To date, most of the studies have been descriptive. For example, the European Childhood Leukaemia-Lymphoma Incidence Study (ECLIS) examined trends in childhood (age 0–14 years) leukemia based on cancer registration data from 23 countries; no significant associations were identified with exposure to radiation from Chernobyl. Other studies have examined changes in leukemia incidence in the Former Soviet Union (FSU) and other European countries. Results from these studies do not provide consistent evidence linking childhood leukemia rates in Europe with radiation exposures due to the Chernobyl accident, but are limited by dependence on historical and current registry data, the quality of which may have changed over time, regional differences in registry operations, and inaccuracy or unavailability of population data. In population studies based on registry data, differences in disease rates in areas characterized by high or low levels of contamination may be due to differences in population characteristics, or extensiveness of cancer registry coverage, rather than the effects of exposure. Only one case-control study has been published, which reports an ~3-fold increase in the risk of leukemia among persons who were 0–20 at the time of the accident (ATA) with highest radiation exposure levels compared with those with the lowest levels, in two regions (oblasts) of Ukraine (Rivno and Zhytomir) contaminated by Chernobyl fallout. Many of the youngest subjects in that study constituted a small subset of a larger ongoing study, the results of which we report here. This larger study was a multi-national population-based case-control study of acute leukemia (AL) diagnosed among children who were <6 years of age ATA conducted in Belarus, Russia, and Ukraine. This study was designed to avoid the principal limitations of descriptive investigations by focusing on complete leukemia case ascertainment and diagnostic verification in defined populations, and individual-level estimates of radiation dose and other exposures of potential aetiological significance.

Methods

Case identification and control selection

Details of the design of this study have been published elsewhere. Briefly, participants were recruited from areas of the FSU that were contaminated by radioactive fallout from the Chernobyl accident (Figure 1). Specifically, leukemia cases and controls were identified from the Gomel’skaya and Mogilevskaya Oblasts in Belarus, the Bryanskaya Oblast in the Russian Federation (the most contaminated oblast in Russia), and the Rovenskaya, Zhytomirskaya, Chernigovskaya, and Cherkasskaya Oblasts in Ukraine (Chernigovskaya and Cherkasskaya Oblasts were on average significantly less contaminated than the Rovenskaya and Zhytomirskaya Oblasts). Cases of AL who were in utero or ≤6 years of age ATA and who were diagnosed in these geographic regions between April 26, 1986 and December 31, 2000, were identified from two types of sources, depending on the circumstances in each republic: records of regional cancer hospitals (oncodispensaries), and population-based tumour registries. In the Russian Federation cases were identified from the Bryansk Oncology Registry. In Belarus cases were identified from the national Belarus Tumor Registry and the Pediatric Oncology Center. In Ukraine cases were identified through manual searches of oncodispensary archival records. Once a potential case was identified, eligibility criteria (i.e. date of birth, date of diagnosis, and residence ATA) were ascertained through review of the medical record (in Russia, these were confirmed by personal interview).

The date of diagnosis of the case was defined as the reference date for purposes of selecting individually matched controls (who were required to be alive on the reference date) and delimiting the time period following the accident for which accumulated individual dose estimates were calculated. In all republics, controls were identified from the records of the oncodispensaries serving the population of each raion included in the study. All records were reviewed to identify potential controls that could be matched to a case on sex, birth year, and raion of residence ATA. However, the protocol for further matching by raion of residence differed between republics (a raion is roughly equivalent to a county in the US). In Russia, controls were matched to cases on raion of residence of the case ATA. In Ukraine, controls were initially matched on raion of residence of the case ATA (118 or 22% of the controls), and subsequently were to be randomly selected from a raion different from that of the case, but within the same oblast. In Belarus, controls were matched to cases on raion of residence on the reference date and randomly selected from any raion of residence ATA with the selection weighted by raion population. A total of 20 potential controls were selected from the polyclinic records for each case and interviews were scheduled for the first two. If the first or second potential controls could not be reached, the next individuals on the list were contacted and scheduled for an interview. This process
was continued until two controls were enrolled in the study for each case.

**Personal interview**

An in-person interview, administered by trained physician and dosimetry interviewers, was conducted for each case and control. Since many of the cases were deceased, interviews were conducted with someone with personal knowledge of the subject’s life up to the reference date, preferably the subject’s mother or another close relative. The interview schedule was developed by both FSU and US scientists and included a demographic questionnaire, general health interview, leukaemia risk factor questionnaire, a brief maternal and paternal occupational history, and a detailed dosimetry questionnaire. The latter instrument included questions related to the sources and consumption of foods and milk; residence and occupation; relocation and migration; personal protective measures after the accident; type of house; and time spent indoors and outdoors after the accident. All procedures and data collection instruments were approved by Institutional Review Boards at the US institutions participating in this research and in Belarus, the Russian Federation, and Ukraine. All study participants provided written informed consent to participate prior to data collection.

**Confirmation of leukaemia diagnoses**

A Leukaemia Diagnostic Working Group (LDWG) consisting of haematologic morphologists and haematologists from Belarus, Israel, Russia, Ukraine, and the United States was created to verify that all cases included for study were indeed AL. Of 463 identified potential cases, a confirmed diagnosis of AL was made in 442 (95%). The potential cases included 77 with no adequate slides available for review, of whom 67 were confirmed as AL and included in this study based on review of clinical information that included the results of laboratory tests, the name of the institution where the diagnosis was made, and whether the patient received therapy. Table 1 summarizes the LDWG consensus diagnosis of the 463 potential cases. The 21 potential cases who were excluded were determined by the LDWG to have the following diagnoses: myelodysplastic syndrome ($n = 4$), chronic myelogenous leukaemia ($n = 4$), other diagnoses ($n = 3$), and no determination ($n = 10$ cases without slides available for review and insufficient clinical information to confirm the diagnosis of AL). Of the 442 confirmed cases, 21 were excluded owing to ineligibility: age $>6$ years ATA or residence outside of the seven study oblasts ATA. Among the 421 cases included in the study were 311 (74%) with acute lymphoid leukaemia (ALL) and 86 with acute myeloid leukaemia (AML) (21%).
distribution of leukaemia subtype is generally consistent with what would be expected based on general population estimates, given the age restriction for inclusion in the present study. A more detailed description of the LDWG results is published elsewhere.20

Dosimetry
Accumulated absorbed radiation dose to the bone marrow and corresponding uncertainties were estimated for each case and matched control from the time of the accident until the reference date. The Dosimetry Working Group comprised of investigators from Belarus, Russia, Ukraine, and the United States developed a common methodology for calculating individualized dose estimates from external radiation fields and from ingestion of contaminated foods. The dosimetry methods reflect changes in external exposure rates and levels of food contamination with time following the accident, as well as local conditions.

The dose estimation methods used individual dosimetry parameters that reflected local conditions at each location where each subject lived during the appropriate time interval. The dosimetry questionnaire described above provided residence history and other pertinent personal information. For study subjects born after April 26, 1986, the mother’s residence and dietary history were also obtained in order to estimate the dose received while the subject was in utero (61 cases). Consumption of mother’s milk by the child through breastfeeding is included when calculating internal doses.

Calculations of external dose for a particular residence location employed data derived from field measurements in the three republics as well as information about individual subjects obtained from the questionnaires. In the first category were data on concentrations of radionuclides in soils, time-dependent exposure rates, shielding factors, and date and times of radioactive cloud arrivals. Soil contamination levels were characterized by the 137Cs deposition density and the ratios of contamination levels relative to 137Cs for other radionuclides separately for each of the raions in the seven oblasts. For each subject, the questionnaire yielded a residence history from the time of the accident to the reference date, type of dwelling at each location, and percentages of time spent outdoors during that period.

The internal dose estimates also relied upon the soil contamination levels at the residence locations. Responses to the questionnaire provided information about individual milk consumption, milk sources and types, and the sources and consumption of other foods. Information based on environmental measurements included raion average soil-to-milk transfer coefficients for radiocaesium (or soil types to estimate such transfer), ratios of 137Cs concentrations measured in various foods to those measured in milk (which changed with time after the accident), the contribution of 134Cs, and losses of radioactivity during food preparation and cooking.

The uncertainties of individual doses were estimated by Monte Carlo simulation of the variability of each of the input parameters used for dose calculations. In order to estimate the uncertainties of individual doses, 1000 realizations of dose calculations were performed on each person using the stochastic variation (distributions) of the input parameters.

Data management and quality assurance
The research team in each country entered the demographic, dosimetric, and other data into a study-specific database designed by the Data Coordination Office (DCO) in Moscow. Data audits

### Table 1 Leukaemia Diagnostic Working Group (LDWG) review diagnoses of 463 potential and 421 included cases

<table>
<thead>
<tr>
<th>LDWG diagnosis</th>
<th>Belarus</th>
<th>Russia</th>
<th>Ukraine</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Potential cases reviewed by LDWG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>90</td>
<td>71</td>
<td>30</td>
<td>61</td>
</tr>
<tr>
<td>AML&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20</td>
<td>16</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>ALU&lt;sup&gt;c&lt;/sup&gt;</td>
<td>11</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total AL</td>
<td>121</td>
<td>96</td>
<td>39</td>
<td>79</td>
</tr>
<tr>
<td>CML&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MDS&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inadequate materials</td>
<td>3</td>
<td>2</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>127</td>
<td>100</td>
<td>49</td>
<td>100</td>
</tr>
<tr>
<td>Included cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>84</td>
<td>74</td>
<td>30</td>
<td>77</td>
</tr>
<tr>
<td>AML&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20</td>
<td>18</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td>ALU&lt;sup&gt;c&lt;/sup&gt;</td>
<td>10</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>114</td>
<td>100</td>
<td>39</td>
<td>100</td>
</tr>
</tbody>
</table>

-<sup>a</sup> Acute lymphoid leukaemia.
-<sup>b</sup> Acute myeloid leukaemia.
-<sup>c</sup> AL, unclassified.
-<sup>d</sup> Chronic myelogenous leukaemia.
-<sup>e</sup> Myelodysplastic syndrome.
were conducted in all three republics to assure the implementation of uniform study methodology across the three study sites (variation in control selection is the exception). Audit procedures included: (i) an assessment of study methodology, involving independent verbal accounts of the research procedures by project managers, interviewers, and data managers; (ii) monitoring interview procedures by conducting duplicate interviews using an abbreviated version of the interview schedule, and (iii) monitoring data entry accuracy by randomly selecting paper records and determining discrepancies between information from paper records and the electronic database. These data were reviewed for quality, consistency, and completeness. Only after all these quality control checks were completed did each team submit its data to the DCO for assembly into a combined file for statistical analyses.

**Statistical methods**

Comparisons of case characteristics between the three republics were based on Pearson’s chi-square test for independence and the median test. Two models were used to examine the relationship between estimated dose and leukaemia risk. In these models the odds of leukaemia for a person with dose \( d \), relative to the odds of an unexposed person \( (d = 0) \), were expressed as a loglinear or linear function of dose, i.e. as either

\[
\text{OR}(d) = \exp\left[\beta_{\text{log}} d\right],
\]

or

\[
\text{OR}(d) = 1 + \beta_{\text{lin}} d,
\]

where the regression parameter \( \beta_{\text{log}} \) or \( \beta_{\text{lin}} \) represents the magnitude and direction of the radiation dose–response. The regression parameter can be defined as a function of other characteristics such as geographical region, sex, or time since the Chernobyl accident, in order to investigate variation of the radiogenic risk with these factors. Since leukaemia is a rare disease, ORs closely approximate relative risks, and \( \beta_{\text{lin}} \) can therefore be interpreted as the excess relative risk (ERR) per unit dose. Estimation of \( \beta_{\text{lin}} \) must be constrained to ensure that \( \text{OR} > 0 \), at least for all values of \( d \) present in the data. This complicates the statistical analysis, e.g. estimation of lower confidence limits, especially for small numbers of matched sets. Therefore the loglinear model was used for most comparisons of subsets. Regression parameters were estimated by the method of maximum likelihood, and their statistical significance tested using likelihood ratio statistics. Since this study sought evidence that radiation exposure increased risk of leukaemia, one-sided tests were used for significance of dose–responses. For all other analyses, two-sided tests were used. 95% confidence intervals (95% CIs) were calculated from the estimated standard error for \( \beta_{\text{log}} \), and from the likelihood for \( \beta_{\text{lin}} \).

**Results**

**Characteristics of cases and controls**

Of the 421 confirmed cases of AL included in the analysis, 44% \( (n = 185) \) were female, the median age ATA (age at the time of the accident) was 2.3 years, and 14% \( (n = 61) \) received at least some in utero exposure (Table 2). Approximately 76% \( (n = 319) \) were born during 1981–85 and nearly half \( (52%; n = 219) \) of the cases were diagnosed before 1991. The median age at diagnosis was ~7 years, and 8% \( (n = 35) \) were diagnosed before 3 years of age. Approximately half of the cases were diagnosed between the ages of 5 and 10. This primarily reflects the restriction of age ATA as an inclusion criterion and is different from what would be expected in an unrestricted sample from a steady-state population. There were no significant differences by country regarding the distribution of sex, year of diagnosis, or age at diagnosis. There was some evidence of heterogeneity of age ATA between the countries \( (P = 0.02) \). However, there was no evidence that the cases from any country tended to be consistently older or younger ATA \( (P = 0.35) \).

Among the 842 controls matched to the 421 included cases, seven were later found to be ineligible and, therefore, excluded from analysis. Interviews were most commonly conducted with the subject’s mother \( (90\% \text{ of cases}, 91\% \text{ of controls}) \) or father \( (5\% \text{ of both cases and controls}) \). Parents’ level of education, an approximate indicator of socioeconomic status, was generally similar between cases and controls, although parents of controls were somewhat more likely to have received college or university education \( (14\% \text{ for both mothers and fathers}) \) than parents of cases \( (9\% \text{ for both}) \).

Diagnostic medical radiation exposures to the head and neck were reported for only four cases \( (1\%) \) and seven controls \( (1\%) \), and histories of dental X-ray exposure were reported for only one case \( (<1\%) \) and five controls \( (1\%) \). Much more common were histories of chest fluoroscopy, reported for 66 cases \( (16\%) \) and 71 controls \( (9\%) \), and other external diagnostic radiation procedures, reported for 57 cases \( (14\%) \) and 79 controls \( (9\%) \). More than half of the cases with histories of chest fluoroscopy had such an examination in the calendar year of the reference date or the preceding calendar year. The same was true of controls. For other external diagnostic radiation exposures, more than half of subjects with such examinations had them in the calendar year of the reference date or in the preceding 2 years \( (cases) \) or 3 years \( (controls) \). The higher frequency of such histories among cases might result at least partly from increased medical attention to cases before their diagnoses of AL. One case \( (<1\%) \) and three controls \( (<1\%) \) had histories of internal \( (oral \text{ or injected}) \) diagnostic radiation exposures. Only four cases \( (1\%) \) and two controls \( (<1\%) \) had any prior history of cancer or other serious diseases, and only one participant, a case, had a history of prior radiation therapy for cancer or any other condition.

**Analyses of estimated doses and dose–response**

Table 3 summarizes the distribution of total estimated radiation dose to the bone marrow calculated using the common methodology, for each country separately and for all countries combined. Overall, the mean dose was higher among cases \( (10.8 \text{ mGy}) \) than controls \( (6.3 \text{ mGy}) \). Mean doses were similar in Belarus and Russia, and there was little difference between cases and controls in these two countries. In contrast, the mean dose for cases in Ukraine was substantially higher \( (10.1 \text{ mGy}) \) than for controls \( (3.5 \text{ mGy}) \), and was somewhat lower than for cases and controls in Belarus and for controls in Russia. There was less difference in median doses between cases \( (0.9 \text{ mGy}) \)
and controls (0.7 mGy), and median doses were considerably lower than the means, reflecting a highly skewed distribution of doses. Median doses were lowest in Ukraine (0.5 mGy for cases and 0.4 mGy for controls) and highest in Belarus (5.6 mGy for cases and 5.0 mGy for controls). It is also evident in the bottom section of Table 3 that a substantially lower proportion of cases, and particularly controls, were in the highest dose category (≥5 mGy) in Ukraine compared with the other two countries.

Analyses of the radiation dose–response are summarized in Table 4. Using <1.0 mGy as the baseline category, the odds ratio for AL was estimated as 1.46 and 2.60 for doses of 1.0–4.999 and ≥5.0 mGy, respectively, for all republics combined. In Ukraine the odds ratio in the highest dose category was 3.50 with 95% CI that

<table>
<thead>
<tr>
<th>Table 2 Characteristics of 421 included leukaemia cases</th>
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<tbody>
<tr>
<td><strong>Belarus (n = 114)</strong></td>
</tr>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td><strong>Age (years) on April 26, 1986 (Age ATA)</strong></td>
</tr>
<tr>
<td>14</td>
</tr>
<tr>
<td>&lt;1</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
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<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Minimum–maximum</td>
</tr>
<tr>
<td><strong>Year of diagnosis</strong></td>
</tr>
<tr>
<td>1986–90</td>
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<tr>
<td>1991–95</td>
</tr>
<tr>
<td>1996–2000</td>
</tr>
<tr>
<td><strong>Age (years) at diagnosis</strong></td>
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<td>1–2</td>
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<td>3–4</td>
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<tr>
<td>5–10</td>
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<tr>
<td>11–15</td>
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<tr>
<td>16–19</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Minimum–maximum</td>
</tr>
</tbody>
</table>

* Based on the Pearson’s chi-square test for differences in proportions and the median test for differences in location.

<table>
<thead>
<tr>
<th>Table 3 Estimated radiation doses, by republic and case–control status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Belarus (n = 114)</strong></td>
</tr>
<tr>
<td><strong>Estimated total dose (mGy)</strong></td>
</tr>
<tr>
<td>Minimum</td>
</tr>
<tr>
<td>Maximum</td>
</tr>
<tr>
<td>Median</td>
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<tr>
<td>Mean</td>
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<tr>
<td>n</td>
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<tr>
<td>&lt;1.0</td>
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<tr>
<td>1.0–4.999</td>
</tr>
<tr>
<td>≥5.0</td>
</tr>
</tbody>
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excludes the value of 1.0 (1.995–6.15). The odds ratios for 
≥5 mGy were also >1.0 for both Belarus and Russia, although 
the corresponding CIs included 1.0. Based on the loglinear model 
for the odds ratio, leukaemia risk increased significantly 
with increasing radiation dose for all republics combined 
(one-tailed $P$-value = 0.0030). This is largely accounted for by 
the significant dose–response in Ukraine ($P$ = 0.005). Although 
the heterogeneity of dose–response among the three republics 
was not statistically significant ($P$ = 0.26), the estimated 
regression coefficient for Ukraine was roughly five times 
greater than the estimate for Belarus. The dose–response was 
not statistically significant in either Belarus ($P$ = 0.33) or 
Russia ($P$ = 0.57).

In order to express the magnitude of the dose–response in a 
more familiar format, the excess relative risk at 1 Gy (ERR/Gy) 
was estimated for each republic and all republics combined. 
For all republics combined the estimated ERR/Gy was 32.4. The ERR/ 
Gy was much larger in Ukraine (78.8) compared with Belarus 
(4.1) and Russia (−4.94). CIs were very wide and overlapped.

The results for Russia in the upper and lower parts of Table 4 
may appear inconsistent, with an odds ratio of 6.0 for the 
≥5 mGy dose category, but a negative slope for the dose– 
response. Such an apparent contradiction can happen with a 
small number of individually matched case–control sets. 
Categorizing doses loses information about the magnitudes of 
differences between matched cases and controls, and in some 
matched sets even the direction of the difference. For example, 
if a case and his/her controls are all within the same dose category, 
they contribute no information to the estimates in the upper part 
of Table 4, but still contribute to either a positive or negative 
estimate of the coefficient in the lower part of the table, 
depending on their doses.

To investigate further the apparent differences in dose– 
response between Ukraine and the other two republics, variation 
of the dose–response across the seven study oblasts was also 
investigated. For this purpose, each case and control was 
classified according to raion of residence ATA, or mother’s 
raion of residence ATA if the subject was in utero ATA. As shown 
in Table 5, only for Rovenskaya Oblast in Ukraine was a 
significant dose–response observed ($P$ = 0.012). The estimated 
dose–response coefficients were largest for Cherkasskaya and 
Chernigovskaya Oblasts: 0.24/mGy and 0.060/mGy, respectively, 
compared with 0.012/mGy for Rovenskaya Oblast. However 
owing in large part to the very low mean doses for 
Cherkasskaya and Chernigovskaya Oblasts, their dose–responses 
were not statistically significant ($P$ = 0.07 for both oblasts). Also 
shown in Table 5 is the ERR/Gy, estimated using the linear 
model. Estimates for the Ukraine oblasts are very large relative to 
those in Belarus, particularly for Rovenskaya and Cherkasskaya 
Oblasts, but the CIs for these estimates are very wide.

In an attempt to better understand the finding of a significant 
dose–response only in the Rovenskaya Oblast, we examined the 
distribution of cases and controls by raion. In Rovenskaya Oblast, 24 
(45%) of the 53 cases lived ATA in relatively heavily 
contaminated raions in the northern part of the oblast (which 
also are characterized by higher transfer coefficients of $^{137}$Cs 
activity from soils to foods), compared with only 13 (12%) of 
the 106 controls. Much of this difference can be attributed to 
two raions that were not relatively heavily contaminated: 
Rovenskii, which includes Rivno City; and Zdolbunovskii, in 
which 10 (19%) of the 53 cases lived ATA, compared with 56 
(53%) of 106 controls. This type of pattern was not observed 
within the other three oblasts in Ukraine, or the two oblasts 
in Belarus.

Table 6 shows the dose–response results separately by sex, 
along with the two-sided $P$-value for the test of significance of 
dose effect modification by sex, based on the loglinear dose– 
response model. There was no significant difference between 
the dose–response in females and males for any republic or all 
republics combined. Similarly, the radiation dose–response did 
not vary significantly in relation to history of prior chest 
fluoroscopy or history of external diagnostic radiation exposures 
other than head and neck, dental X-ray, and chest fluoroscopy, 
and there was also no significant trend of increasing or decreasing 
dose–response with age ATA (data not shown).

Discussion
This is the first reported population-based study of childhood 
leukaemia among persons exposed to radiation from the 
Chernobyl accident conducted in the contaminated regions of
Ukraine, Belarus, and Russia using a common methodology and based on individual estimates of radiation dose. We report two principal findings. First, the magnitude of the radiation doses received by study participants was relatively low. Median doses in all three countries were <10 mGy, and mean doses were <15 mGy. These doses were much lower than originally expected, although not inconsistent with earlier estimates of average exposure. Second, there was an overall significant increase in leukaemia risk associated with increasing radiation dose to the bone marrow. This association was most evident in Ukraine, where there appeared to be a disproportionate number of controls from less heavily contaminated raions, but was also apparent (but not statistically significant) in Belarus. There was no evidence of a radiation dose–response relationship in Russia, but the number of leukaemia cases in the study from Russia was quite small compared with the other two countries.

It is well established that exposure to ionizing radiation can increase the risk of leukaemia. Most of the evidence derives from studies of external exposure to low-LET radiation at high dose rates. The most comprehensive assessment of radiation-induced leukaemia is from long-term studies of survivors of the atomic bombings in Hiroshima and Nagasaki. However, it is important to recognize that the exposure circumstances in Japan were very different from Chernobyl, most notably regarding dose rate (nearly instantaneous exposure in Japan) and dose level (average doses to A-bomb survivors were ~0.25 Sv). Based on recent analyses of incidence data, the ERR of all types of leukaemia at 1 Sv is estimated to be 4.37. This estimate is higher for persons exposed under age 20 (6.11), and considerably higher when restricting the analysis to cases that develop within 5–10 years from exposure (18.69). Results are similar based on mortality data, with an overall ERR per Sv of 4.62. There is strong evidence of non-linearity in the dose–response for leukaemia in the A-bomb survivor data, with estimates of risks at 0.1 Sv being ~1/20th of those at 1 Sv. Estimates of total dose to survivors in Hiroshima, moreover, include neutron contributions of 10–20% (assuming an RBE of 10 for neutrons).

The other principal source of information regarding the effects of radiation exposure on leukaemia risk in humans comes from studies of persons exposed for medical reasons. Several large follow-up studies have been conducted of cohorts exposed therapeutically to external low-LET radiation, most notably to treat ankylosing spondilitis, cervical, uterine, and breast cancer, tinea capitis, tuberculosis, and benign gynaecological disease. These studies are also characterized by doses considerably higher than those considered in the present study (average doses for the studies referenced above range from ~0.3 to several Sv), and by relatively high dose rates (dose delivered over a very short time). ERR estimates at 1 Sv from these investigations range from 0.17 to 6.0, with considerable variation. Owing to the nature of the radiation exposure in these studies, results at 1 Sv are comparable with those at 1 Gy in the present investigation.

In contrast to these findings, no consistent evidence of an increased risk of leukaemia associated with exposure to radiation from Chernobyl has yet been reported. The one case–control study that reported an excess of leukaemia among persons 0–20 ATA in Ukraine included a small subset of the present
study, and radiation doses were estimated for only one-third of the cases and a lesser proportion of controls. It is not clear how the selection of cases and controls for dose estimation was done, and whether it was accomplished in an unbiased manner. There is also no consistent evidence from studies of populations with exposure circumstances that might be somewhat similar to those experienced at Chernobyl. Although there is some evidence of a possible increase in leukaemia among persons living near the Techa River in the southern Urals who received both internal and external exposures from the nearby Mayak nuclear facility (average dose of \(~0.5\) Sv), a number of questions remain regarding the adequacy of the dosimetry and the methods of case ascertainment. Findings from studies of occupational exposures, which are relatively low and more protracted over time, are inconsistent and inconclusive. Similarly, studies of populations living in areas with high background radiation levels have not demonstrated a clear increase in the occurrence of leukaemia.

The point estimates of risk from the present study overall and for Ukraine specifically are much larger in magnitude than the range of estimates reported from studies of persons exposed to much larger doses at higher dose rates, but given the wide CIs are not inconsistent with such estimates. No estimates of similar magnitude have been reported from studies of populations exposed to the lower doses or dose rates that characterize the populations exposed around Chernobyl. Thus, given the inconsistency of the present findings with existing estimates of radiation-associated leukaemia, and the lack of consistency of findings across the three countries, additional analyses were conducted to investigate the potential effects of two aspects of the study methodology that might influence these results. First, we repeated the analysis after excluding cases diagnosed within 5 years after the Chernobyl accident to allow for a period of latency after the start of exposure, as there is some evidence to suggest that the peak occurrence of leukaemia after radiation exposure is \(~5\) years. The dose–response results were not materially changed by excluding the first 5 years’ cases from those in Tables 4 and 5. In fact the estimated radiation dose–response did not vary significantly as the interval of time from the accident to the diagnosis of leukaemia increased (Table 7).

Second, we considered the potential impact on the dose–response results of the method of selecting controls, which was somewhat different in Ukraine than in Belarus or Russia. The exclusion of the case raion for selecting the majority of the controls in Ukraine could potentially result in a systematic tendency to select controls from less contaminated areas than cases, particularly when a case is from a more highly contaminated area and given that there are substantially more raions with lower contamination levels than higher contaminated areas, given that there are substantially more raions in the oblasts included in the study, and may have resulted in an overestimate of leukaemia risk. There is some evidence of this occurring in the Rozenskaya Oblast. The method of selecting controls used in Belarus is less likely to result in a similar tendency because a much higher proportion of the raions in the oblasts included from Belarus are relatively heavily contaminated and because controls were selected based on the population distribution by raion. Other possible factors that might explain, at least in part, the different results in Ukraine could be different underlying susceptibility to the effects of radiation exposure in the study population or systematic differences in the dose estimates.
are highly susceptible, or that they include a highly susceptible subpopulation large enough to account for these results. Because a common method is used to estimate individual radiation doses in all three republics, it is also unlikely that there is a systematic difference in dosimetry between Ukraine and the other two countries that could account for these results. This would require that there be differences in the underlying dosimetry data that are inputs to the model, or that dosimetry differences exist within the Ukraine, between Ukrainian cases and controls, or perhaps between raions.

It should also be noted that because radiation doses were very low, and much lower than originally anticipated, the statistical power of the study was substantially reduced. The mean and variance of the estimated doses for all 1256 cases and controls in this study were 8 mGy and 688 mGy², respectively. This implies that testing whether the dose–response regression parameter β_{log} in the loglinear model is greater than zero has power of ~84% under the alternative hypothesis β = 0.006/mGy, which corresponds to an ERR of 6.1 at 1 Gy (one-sided test at 5% critical level). While this level of statistical power might be acceptable in the context of acute external exposures to relatively high doses, it does not ensure with a high degree of confidence that effects of smaller but, nevertheless, appreciable magnitude (an ERR/Gy of <.61), as might occur following prolonged exposure to smaller doses, will be detected.

This study has a number of strengths. It is population-based, with a high degree of completeness of case ascertainment, and all cases of leukaemia were independently verified by an expert panel of morphologists and haematologists. It is focused on the cases of leukaemia were independently verified by an expert with a high degree of completeness of case ascertainment, and all exposure to smaller doses, will be detected.

This study is a number of strengths. It is population-based, with a high degree of completeness of case ascertainment, and all cases of leukaemia were independently verified by an expert panel of morphologists and haematologists. It is focused on the effects of exposure during childhood, which is considered to be the period of highest risk of radiation-induced leukaemia, and is relatively large (421 cases and nearly twice as many controls). Risk estimates are based on individual estimates of radiation dose from Chernobyl for each study participant. Common and standardized methods of data collection and dose estimation were used in all three countries, and extensive data quality control and auditing procedures were employed.

In summary, this study found that: (i) the magnitude of the radiation doses received by study participants was relatively low; and (ii) that there was an overall significant increase in leukaemia risk associated with increasing radiation dose to the bone marrow, which was most evident in Ukraine. These findings, taken at face value, suggest that prolonged exposure to very low radiation doses may increase leukaemia risk as much as or even more than acute exposure, but are inconsistent with published literature regarding the risk of leukaemia in relation to protracted radiation doses of the very low magnitude observed in this study. The large excess risks and significant dose–response observed in this study might be accounted for, at least in part, by an overestimate of risk in Ukraine. Therefore, we conclude that this study provides no convincing evidence of an increased risk of childhood leukaemia as a result of exposure to Chernobyl radiation, since the extent to which the association found is owing to a sampling-derived bias in Ukraine, rather than a radiation-related excess, is unclear. However given the very low estimated radiation doses and resulting low statistical power, the lack of significant dose–responses in Belarus and Russia also cannot convincingly rule out the possibility of an increase in leukaemia risk at low dose levels.

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