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Permalink

<https://escholarship.org/uc/item/9mn2p2jw>

Journal

The Lancet Haematology, 5(8)

ISSN

2451-9960

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Publication Date

2018-08-01

DOI

10.1016/s2352-3026(18)30092-9

Peer reviewed



Published in final edited form as:

Lancet Haematol. 2018 August ; 5(8): e346–e358. doi:10.1016/S2352-3026(18)30092-9.

Leukaemia and myeloid malignancy among prospectively analysed cohorts of persons exposed to low doses (<100 mSv) of ionising radiation at ages under 21 years

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Contributors

MPL/ABdG/MSL conceived and designed the study, and produced an analytical plan. MPL was responsible for acquisition/processing of data and for analysis. DB/CL critically assessed the dosimetry. MPL/RW/ABdG/MSL interpreted the results. MPL produced a first draft of the manuscript. All authors reviewed the manuscript and provided intellectual input.

DECLARATION OF INTERESTS

RW is a member of the Technical Working Party of the UK Compensation Scheme for Radiation-Linked Diseases and advises the Tokyo Electric Power Company on radiological protection matters.

All other authors declared no conflicts of interest.

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Abstract

Background—Substantial evidence links exposure to moderate/high doses of ionising radiation, particularly in childhood, with leukaemia risk. The relation with low-dose (<100 mSv) exposures is less certain, but this is the dose-range most relevant to the general population. We aimed to estimate radiation-associated risk of leukaemia after low-dose exposure in childhood (age <21 years).

Methods—Since highest radiation-related leukaemia risks follow childhood exposure, we pooled eligible cohorts with age at first irradiation <21 years, restricting analysis to individuals with mean cumulative active bone marrow doses <100 mSv. We excluded groups treated for malignant disease. We evaluated leukaemia and myeloid malignancy outcomes based on harmonised International Classification of Diseases/ International Classification of Disease for Oncology classifications. Dose-response models were fitted using Poisson regression. All data were fully blinded for the purposes of the statistical analysis.

Findings—In 9 eligible cohorts 262,573 persons exposed to <100 mSv accrued 154 myeloid malignancies (including 79 acute myeloid leukaemias, 8 myelodysplastic syndromes and 36 chronic myeloid leukaemias) and 40 acute lymphoblastic leukaemias. The fitted relative risks at 100mSv were: 3.09 (95%CI: 1.41, 5.92, *p-trend*<0.01) for acute myeloid leukaemia plus myelodysplastic syndromes; 2.56 (95%CI: 1.09, 5.06, *p-trend*=0.03) for acute myeloid leukaemia; and 5.66 (95%CI: 1.35, 19.71, *p-trend*=0.02) for acute lymphoblastic leukaemia. There was no clear dose-response for chronic myeloid leukaemia (*p*=0.39). There were few indications of inter-cohort heterogeneity or departure from linearity. For acute myeloid leukaemia plus myelodysplastic syndromes and for acute lymphoblastic leukaemia the dose-responses remained statistically significant (*p*<0.05) for doses <50 mSv. Excess absolute risks at 100 mSv were in the range 0.1–0.4 cases/deaths per 10,000 person-years.

Interpretation—In this pooled analysis we have shown that risks of acute myeloid leukaemia and acute lymphoblastic leukaemia were significantly elevated after cumulative doses of ionising radiation <100 mSv received in childhood/adolescence, with excess risk also apparent <50 mSv for some endpoints. The risks are somewhat higher than, but compatible with, those seen in other studies with cumulative doses and dose rates both higher and lower than those studied here. These findings suggest that there is risk of leukaemia associated with low-level exposure to radiation, and implies that the current system of radiological protection is prudent and not overly protective.

Keywords

leukaemia; acute myeloid leukaemia; acute lymphoblastic leukaemia; myelodysplastic syndromes; myeloid malignancies; ionizing radiation; low dose risk; medical radiation exposure; atomic bomb survivors

INTRODUCTION

Leukaemia is the main sentinel radiogenic malignancy; the red (active) bone marrow is among the most radiosensitive of any organ or tissue, and leukaemia generally appears sooner than any other cancer after exposure to ionising radiation¹. At moderate-to-high doses (>0.5 Sv) there is abundant evidence of radiation-related excess risk for most major leukaemia subtypes, in particular acute myeloid leukaemia, and chronic myeloid leukaemia, and to a lesser extent acute lymphoblastic leukaemia¹. There is little evidence of an association with chronic lymphocytic leukaemia¹, now classified as a non-Hodgkin lymphoma². There is emerging evidence of radiogenic risk associated with myelodysplastic syndromes, a myeloid-lineage precursor to acute myeloid leukaemia³. Particularly high excess relative risks of subsequent leukaemia have been reported following radiation exposure in childhood¹. Evidence of risk at lower doses is less well established, in particular at radiation doses to the active bone marrow (ABM) of 100 mSv or less (the level of dose often used to demarcate low dose^{1,4}), with some claiming a threshold for leukaemia and other cancers, below which there is no excess cancer risk⁵. Most population exposures are from natural background radiation, diagnostic medical tests, or occupational, and are typically low doses⁶, so evaluating risks in this dose range is critical for radiation-protection purposes.

Because radiation exposure in childhood has been shown to confer the highest proportionally increased risks for subsequent leukaemia¹, which are also higher than for any other malignancy, individuals with childhood exposures afford the best opportunity for studying low-dose cancer risks. Leukaemias are a rare cancer type and most individual studies do not have sufficient numbers of cases that have received low-dose ionising radiation exposure to provide adequate statistical power to estimate risk accurately. To directly evaluate low dose leukaemia risk, we have therefore conducted a pooled analysis of eligible cohorts that have received radiation exposure at a young age to assess risks of leukaemia following low-dose (<100 mSv) exposure to external sources of (predominantly photon) radiation, generally for medical diagnosis or treatment of benign conditions; lymphomas and multiple myeloma were not included because of evidence that these diseases have limited sensitivity to induction by radiation¹. We excluded any groups treated for malignant conditions, in which chemotherapy would potentially be a strong confounder. Particular emphasis was placed on known radiogenic leukaemia subtypes, specifically (a) acute myeloid leukaemia with/without myelodysplastic syndromes, (b) chronic myeloid leukaemia, (c) acute lymphoblastic leukaemia. We also evaluated acute leukaemia and all leukaemia excluding chronic lymphocytic leukaemia for comparison with groupings used in earlier studies, and to include leukaemias (excluding chronic lymphocytic leukaemia) that are otherwise unspecified. The primary hypothesis was that radiation would increase risk of all radiogenic leukaemia even at low doses.

METHODS

Study design and participants

Overall study design—We examined all available cohort studies reporting on or before 30th June 2014, with 5 leukaemias or other myeloid malignancies receiving mean

LSS cohort (1 October 1950). Follow-up in the UK-NCI CT study started at the date of the first CT. More detailed information on dates of entry are given in Web-appendix p. 12.

Further details of the study cohorts are given in Web-appendix pp. 2–3, and of follow-up in the individual cohorts in Web-appendix p. 4. The protocol was finalised on 21st March 2016.

Randomization and masking

All data received by the statistical analyst (MPL) was in fully anonymised form.

Procedures

Radiation dosimetry—Cumulative doses averaged over the whole-body ABM were calculated for each subject in the cohorts according to methods described previously. A variety of different methods were used in the component cohorts, but most other than the LSS were based on medical record abstraction of the original treatments (including descriptions of treatments received) and relevant patient data. For the Massachusetts TB, Canadian TB, LSS, US spinal curvature, and UK-NCI CT cohorts Monte Carlo simulated dosimetry was used, while for all other cohorts a methodology based on physical measurements was used to estimate doses. The LSS dosimetry was particularly complex, accounting for both the source terms, radiation transport through air, shielding by terrain and physical structures and by the body itself¹⁸. Doses were expressed as equivalent doses in Sv. Further details are given in Web-appendix pp. 5–7. The pooled analysis generally used the most recently calculated set of doses described in these studies, specifically the DS02R1 with corrections to Hiroshima and Nagasaki map coordinates and terrain shielding, as employed in the latest analysis of the LSS cancer incidence data¹⁴.

Outcomes

Identification and classification—The methods/sources of case identification were study-specific. These included: (1) tumour/cancer registries (LSS, UK-NCI CT, Göteborg and Stockholm haemangioma); (2) medically validated self-reported incidence information (French haemangioma); (3) national and regional cause of death registers (Canadian and Massachusetts TB fluoroscopy, US scoliosis, Rochester thymus). The groups of malignancies considered in this study were those for which there was previous evidence of radiogenicity¹. The number of myelodysplastic syndrome cases/deaths (8) was insufficient to evaluate risk. Myelodysplastic syndromes were, however, included in analyses combined with acute myeloid leukaemia to reflect recognition of myelodysplastic syndromes (previous nomenclature “refractory anaemia”) as a neoplasm and a frequent precursor of acute myeloid leukaemia based on the WHO 2001 classification²; myelodysplastic syndromes were also included in the group of all myeloid malignancies. As these studies span several decades, during which there have been major changes in classification of leukaemia/myeloid neoplasms, and included both incidence (5 cohorts) and mortality (4 cohorts) data, we carefully reviewed each of the outcomes and developed leukaemia/myeloid disorders groupings (based on International Classification of Diseases (ICD) and International Classification of Diseases for Oncology (ICD-O) codes) that were relatively homogeneous over calendar time and across studies, and were consistent with newer categories based on the World Health Organization (WHO) 2001 Classification². The ICD and ICD-O disease

endpoints are specified in Web-appendix pp. 8–9. All disease coding was centrally reviewed by MPL and MSL in conjunction with individual cohort investigators. The principal risk estimate in each instance was the relative risk (RR) of developing specific types of leukemia or myeloid neoplasms or groupings of these outcomes based on the ionising radiation dose response. However, we also evaluated the excess absolute risk associated with radiation exposure.

We defined the following outcomes of interest, primarily focused on the main radiogenic leukaemia malignancies, specifically (a) acute myeloid leukaemia combined with myelodysplastic syndromes, (b) acute myeloid leukaemia, (c) chronic myeloid leukaemia, and (d) acute lymphoblastic leukaemia. For comparison with older studies, we evaluated acute leukaemia and all leukaemia excluding chronic lymphocytic leukaemia, which also included, as appropriate, unspecified leukaemias; chronic lymphocytic leukaemia, now classified as a form of non-Hodgkin lymphoma, was excluded as there is little evidence that it is radiogenic¹. Deaths were coded to the ICD revisions 6 through 10, and incident outcomes were generally coded to the ICD-O revisions 2 or 3 (see Web-appendix pp. 8–9, for detailed ICD/ICD-O coding)².

Statistical analysis

The key covariates evaluated in individual cohorts and in the pooled analysis were selected because they are known to modify leukaemia risk or were potentially important effect modifiers¹ and were available from all of the cohorts. The covariates included sex, age at entry, age first exposed to radiation, age last exposed, age attained, year of birth, years since first exposure, years since last exposure, and two-year lagged mean ABM dose accumulated in moving windows by time since exposure/age at exposure.

The primary hypothesis was that radiation would increase risk of all radiogenic leukaemia even at low doses. Accordingly, the primary model used for reporting results was the linear relative risk (RR) model, a model that has been found to fit radio-epidemiological data well at low doses¹. We estimated the RR at 100 mSv of mean cumulative ABM dose (RR/100 mSv) for each outcome via the fit of the continuous dose-response model, and also assessed the RR for pre-defined dose-categories using the unexposed group (0 mSv) as the reference category. We compared the fit of linear and linear-exponential models in dose to determine whether there was possible non-linearity of RR with dose. We also assessed whether the risk varied with time since exposure or age at exposure. Mean cumulative ABM doses were lagged by 2 years, chosen *a priori*¹, but a sensitivity analysis was conducted assessing lags of 0, 5 and 10 years. The statistical power using a 1-sided Poisson trend test with type-I error $\alpha=0.05$ ¹⁹ and risk coefficients derived from the subset of the publicly available LSS dataset of Hsu *et al*¹⁴ with age at exposure <20 [ERR/Sv =11.32 for acute myeloid leukaemia, =6.89 for chronic myeloid leukaemia, =21.87 for acute lymphoblastic leukaemia], with the given numbers of leukaemias and using the dose distribution outlined in Table 1, was 45.3% for acute myeloid leukaemia, 17.5% for chronic myeloid leukaemia and 53.3% for acute lymphoblastic leukaemia.

The models were fitted by Poisson maximum likelihood²⁰ using Epicure²¹ and R²². Tests for trend used the likelihood ratio test²⁰. All models were stratified by cohort, sex (male/

female/unknown), age (0 / 5 / 10 / ... / 95 / 100 / >100 years), calendar period of observation (1900 / 1910 / 1920 ... / 1990 / 2000 / 2010 / 2016), and radiation dose (0 / 0.005 / 0.01 / 0.02 / 0.05 / 0.10 Sv). Although not used in the final analysis, the cohort was also stratified by certain other variables (years from first exposure, years from last exposure, age at entry, entry year, years from study entry); further details are given in Web-appendix p. 10. Likelihood-ratio tests of heterogeneity²⁰ across datasets were used, testing statistical compatibility of the RR at 100 mSv (which we shall write henceforth as RR/100 mSv) in each dataset against the common RR/100 mSv in the remaining eight cohorts, for each endpoint. GAMs were also fitted¹⁷, in order to assess the magnitude of the excess absolute risk (EAR), i.e. the radiation-associated extra cases/deaths per person and year of follow-up, for each outcome and cohort. Further statistical details are given in Web-appendix p. 28.

Role of the funding sources

The funding sources had no role in: study design; data collection, analysis, and interpretation of data; writing of the report; or the decision to submit the paper for publication. Only MPL, JSM and DC had access to the complete raw data. The corresponding author (MPL) had full access to all of the data and the final responsibility to submit for publication.

Ethical approval

The study cohort has been declared exempt by the National Cancer Institute Special Studies Institution Review Board, because using pre-existing approved data.

RESULTS

The combined nine cohorts included 262,573 persons in the studied dose range from 0 to 100 mSv, accumulating 5,154,464 person-years of follow-up (Table 1); of 262,573 persons in the cohort, 132,706 (50.5%) were male and 129,645 (49.4%) were female (Table 1). Among the exposed the person-year-weighted mean cumulative ABM dose was 24.0 mSv, the cohort means having a range 10.2–52.0 mSv (Web-appendix p. 12). The mean age at first exposure was 9.13 years (cohort mean range, 0.11–18.16 years), and the mean years since last exposure was 22.17 years (Web-appendix p. 12); 3,509,217 (68.1%) of 5,154,464 person-years of follow-up were accumulated with mean lagged ABM dose <10 mSv (Table 1). There were 154 myeloid malignancies, including 79 acute myeloid leukaemia, 36 chronic myeloid leukaemia and 8 myelodysplastic syndromes, and also 40 acute lymphoblastic leukaemia. The grouped categories used for comparisons included 139 acute leukaemia and 221 leukaemias excluding chronic lymphocytic leukaemia.

There were significant linear dose-response relationships for acute myeloid leukaemia +myelodysplastic syndromes, acute myeloid leukaemia, and acute lymphoblastic leukaemia (Table 2). The fitted RR/100 mSv were: 3.09 (95% CI 1.41, 5.92, *p-trend*<0.01) for acute myeloid leukaemia+myelodysplastic syndromes; 2.56 (95% CI 1.09, 5.06, *p-trend*=0.03) for acute myeloid leukaemia; and 5.66 (95% CI 1.35, 19.71, *p-trend*=0.02) for acute lymphoblastic leukaemia. There was little evidence of a dose-response for chronic myeloid leukaemia. The dose-responses are depicted graphically in Figure 1. For no endpoint was there significant curvilinearity (*p*>0.15) (Web-appendix p. 13), nor was there for the

medically-exposed groups of diagnostic and therapeutic studies considered separately ($p>0.10$) (results not shown).

Table 3 suggests that for acute myeloid leukaemia+myelodysplastic syndromes and acute lymphoblastic leukaemia there were statistically significant dose-response relationships for doses <50 mSv, with fitted RR/100 mSv 4.88 (95% CI 1.79, 10.17, p -trend <0.01) and 11.52 (95% CI 1.99, 45.45, p -trend=0.02), respectively, and for acute lymphoblastic leukaemia there was a significant dose-response at <20 mSv, with fitted RR/100 mSv 45.09 (95% CI 7.86, 192.50, p -trend <0.01). For some outcomes, the negative excess relative risk (ERR) derived from the fitted model means that the predicted RR/100 mSv ($= 1 + \text{ERR} \times 0.1$) becomes negative, and when this occurred we set the predicted RR/100 mSv to zero (see Web-appendix p.28).

We examined the effect of time since exposure and age at exposure for the endpoints with evidence of a significant dose-response. Although there were indications for all these endpoints of a reduction of relative risk with increasing time since exposure, the trends were not statistically significant ($p>0.2$) (Web-appendix pp. 14–15). There was no clear trend in risk with age at exposure (Web-appendix pp. 16–17), and there was no indication of modification of risk by duration of exposure (Web-appendix p. 18).

For the grouped disease categories (acute leukaemia, all leukaemia excluding chronic lymphocytic leukaemia), there was a significant linear dose-response relationship for acute leukaemia with a fitted RR/100 mSv of 2.70 (95% CI 1.40, 4.71, p -trend <0.01) (Table 2) and a statistically significant dose-response relationship at <50 mSv but not at <20 mSv (data not shown), while for leukaemia excluding chronic lymphocytic leukaemia there was a borderline significant increasing trend with dose with a fitted RR/100 mSv of 1.84 (95% CI 0.97, 3.08, p -trend=0.06) (Table 2). There was no evidence of curvilinearity for either of these grouped endpoints, nor was there for the groups of diagnostic and therapeutic studies considered separately ($p>0.5$) (results not shown).

Accounting for dose in the period 2–5 years before the point of evaluation of risk significantly improved the model fit over that for dose received ≤ 5 years for acute myeloid leukaemia+myelodysplastic syndromes, acute lymphoblastic leukaemia, acute leukaemia and leukaemia excluding chronic lymphocytic leukaemia (all $p<0.05$), and resulted in marginally significant improvements in model fit ($0.1>p>0.05$) for all myeloid neoplasms and acute myeloid leukaemia (Web-appendix p. 19). There were indications ($p\approx 0.05$) that accounting for dose in the period 0–2 years before point of risk improved the model fit for all myeloid neoplasms, acute myeloid leukaemia+myelodysplastic syndromes and acute myeloid leukaemia (Web-appendix p. 19). In general, the effect of increasing the dose lag period was to decrease the RR and increase the associated p -value, but for acute lymphoblastic leukaemia increasing the lag from 0 year to 2 years resulted in a notably increased RR (relative to that using the 0 year lag) that became significant (Web-appendix p. 20).

There was little evidence of inter-cohort heterogeneity in risk, with only 3 of the 63 tests with adequate convergence exhibiting statistically significant ($p<0.05$) heterogeneity (Web-

appendix p. 21). More detailed investigation of heterogeneity between the LSS cohort and all the combined other cohorts in Web-appendix p. 22 did not suggest any marked discrepancy in risks between the LSS and all other cohorts for any endpoint ($p>0.25$), although risks were somewhat higher in the combined medical cohorts than in the LSS for all myeloid endpoints (acute myeloid leukaemia+myelodysplastic syndromes, acute myeloid leukaemia, chronic myeloid leukaemia) and for the grouped category acute leukaemia, but lower than LSS risks for acute lymphoblastic leukaemia and leukaemia excluding chronic lymphocytic leukaemia. There was no further suggestion of heterogeneity ($p>0.25$) if there was further breakdown of the medical cohorts when grouping by therapeutic and diagnostic exposure (Web-appendix p. 23), although there were indications for most endpoints that risks were slightly higher in the diagnostic group than in the therapeutic group, and both tended to be higher than those in the LSS. In addition, although there were indications of higher risk for mortality compared with incidence for most malignant endpoints (with the exception of acute lymphoblastic leukaemia and leukaemia excluding chronic lymphocytic leukaemia), the differences were not statistically significant ($p>0.10$) (Web-appendix p. 24).

Excess absolute risks were generally small in our study: in the range 0.1–0.4 cases/deaths per 10,000 person-years at 100 mSv (Web-appendix p. 25); it should be noted that some of the models did not converge for the rarer endpoints.

We also analysed the magnitude of the variation of baseline absolute risk by cohort (using the LSS as the reference cohort) (Web-appendix p. 26); there was no significant variation between the cohort baseline risks for leukaemia excluding chronic lymphocytic leukaemia ($p=0.52$), although there were indications of differences for acute myeloid leukaemia ($p=0.02$) and acute myeloid leukaemia+myelodysplastic syndromes ($p=0.03$). There were consistent relative elevations in the baseline risks for the Göteborg haemangioma and US scoliosis cohorts for all three of these endpoints; otherwise, the variations were relatively modest. Although not shown in Web-appendix p. 26, because of non-convergence, there were only weak indications of heterogeneity of baseline risk by cohort for acute lymphoblastic leukaemia ($p=0.31$) and chronic myeloid leukaemia ($p=0.07$).

DISCUSSION

In this pooled analysis of leukaemia and myeloid malignancies in nine cohorts of those exposed in childhood or adolescence to ionising radiation with mean cumulative ABM doses <100 mSv we observed a significant linear dose-response for acute myeloid leukaemia (with or without myelodysplastic syndromes), acute lymphoblastic leukaemia and the grouped category of acute leukaemia. A cumulative ABM dose of 100 mSv in childhood/adolescence resulted in the risks of acute myeloid leukaemia (with or without myelodysplastic syndromes) and acute leukaemia increasing by factors of ~2.6 to 3.1, and the risk of acute lymphoblastic leukaemia increasing by a factor of ~5.7 (Table 2). For acute myeloid leukaemia+myelodysplastic syndromes, acute lymphoblastic leukaemia and acute leukaemia, risks were significantly elevated also at <50 mSv, and for acute lymphoblastic leukaemia at <20 mSv (Table 3). Because these diseases are rare the excess absolute risks were small, in the range of 0.1–0.4 excess cases/deaths per 10,000 person-years at 100 mSv. There was no significant trend with dose for chronic myeloid leukaemia, which is known to

be radiogenic¹; the relatively small number of such cases (36) and limited statistical power to assess risk at low doses may be a factor in the lack of significant trend of this endpoint here, due to the limited follow-up in these cohorts at the ages when chronic myeloid leukaemia would be most expected¹.

Although there have been previous pooled analyses of radiation exposure and leukaemia risk (e.g., Little *et al.*²³, Leuraud *et al.*²⁴) this study is, to the best of our knowledge, the first to estimate risks of leukaemia and myeloid neoplasms following exposures to low levels of radiation during childhood and adolescence. This is the exposure range that is relevant for most people as described above⁶ but where risks remain uncertain. In contrast to previous pooled analyses, we also incorporated a critical evaluation of the ABM dosimetry. We focused on categories of leukaemia and myeloid neoplasms consistent with the WHO 2001 classification² but also evaluated earlier disease categories that allowed us to compare with previous outcome groupings.

Previous low-dose studies have included those of childhood leukaemias associated with natural background exposure, the results of those recently conducted in UK²⁵, Switzerland²⁶, Finland²⁷ and France²⁸ being compatible with the RR estimates presented here, as can be seen from the degree of overlap of the confidence intervals with central estimates in Web-appendix p. 27. There have been a number of other studies of low dose-rates (but not necessarily low cumulative doses) of environmental radiation exposure of children and adults. Children exposed to low ABM doses as a result of the Chernobyl nuclear accident have been investigated²⁹, and although some aspects of these studies (as highlighted by the authors) have been problematic, particularly the methods of control selection and the potential for recall bias, the leukaemia risks are compatible with those reported here (Web-appendix p. 27). The leukaemia RRs observed in residents near the contaminated Techa River in Russia (with 72 cases of leukaemia excluding chronic lymphocytic leukaemia among those exposed at all ages), in a small study of persons exposed to ⁶⁰Co-contaminated steel in apartment buildings in Taiwan (with 11 cases of leukaemia excluding chronic lymphocytic leukaemia among those exposed at all ages), and in another small study of residents of a high-natural background area in India (with 20 cases of leukaemia excluding chronic lymphocytic leukaemia among those exposed at all ages) are also consistent with the present findings (Web-appendix p. 27), although these studies generally have had limited power because the numbers of persons exposed at a young age have been relatively small¹⁹ compared to our pooled analysis. In addition, there have been many studies examining effects of medical diagnostic exposures in the perinatal period in which doses were generally low (<0.1 Gy), but results have been difficult to interpret reliably³⁰, and in many instances these studies have lacked statistical power. However, studies of protracted low-dose, low-dose-rate radiation exposures of workers -although not involving childhood/adolescent exposures -have also shown increased leukaemia risks, particularly chronic myeloid leukaemia^{24,31} (Web-appendix p. 27). In summary, in most of these other low-dose or low dose-rate studies there are indications of radiation-associated excess leukaemia risk, even where these are not conventionally statistically significant, with risk estimates that are compatible with our own.

To the best of our knowledge, all of the substantial cohort studies of leukaemia after low-dose exposure in childhood/adolescence that meet the eligibility criteria (see Web-appendix pp. 2–3 for details of the few excluded studies) have been included in this analysis. One limitation of this study is that the dosimetry was not uniform between the cohorts, as discussed in Web-appendix pp. 2–3, 5. Although the cohorts were exposed at low cumulative doses (<100 mSv) when averaged over all ABM compartments, consideration must be given to the heterogeneity in ABM dose (due to the specificity of the anatomic sites undergoing diagnostic examination or treatment) for all cohorts apart from the LSS. Therefore, a mean cumulative ABM dose of 100 mSv could potentially, in some of the therapeutically-exposed cohorts, e.g., the haemangioma cohorts^{11,12}, imply appreciably higher doses, some >1 Gy in certain bone marrow compartments, but a more detailed investigation of compartmental bone marrow doses would be needed to fully elucidate this. However, this heterogeneity would only matter if there was appreciable non-linearity in the leukaemia dose-response in this dose range, but we found no indication of this. The evidence is that if risks are being driven by anything in the non-LSS cohorts it is by the diagnostically-exposed groups, as is clear from Web-appendix p.23 -- in general risks in the therapeutically-irradiated cohorts are less than those in diagnostically-exposed groups. Overall, the risk coefficients in the medically-exposed cohorts were, in general, slightly higher than, but statistically compatible with, those in the LSS (Web-appendix pp. 22–23), suggesting that the effect of any such non-linearity in dose response is slight.

The cohorts had a follow-up period extending over many years, in some groups from the early part of the last century. As a consequence, another limitation of this study is that disease coding may not be uniform even within a study or across countries. However, there was little evidence of this in aggregate – the variation in baseline risks between cohorts was modest, even where statistically significant (Web-appendix p. 26). In general, misclassification of a highly radiogenic outcome such as leukaemia would be expected to bias risk estimates towards the null, if non-differential with respect to exposure. Bias would not be expected if misclassification was only due to variations in sensitivity (e.g., for myelodysplastic syndromes, which were not diagnosed or reported during the early study periods). The relative risk models we used were stratified by cohort, and so *a fortiori* by country, and by calendar period, thus accounting for differences in baseline rates between countries, or over time, or both; however, more subtle variations in diagnosis would not have been captured by our modeling. The mixture of mortality and incidence data also complicates the interpretation because, *inter alia*, there was generally increasing treatment success over time, which was not uniform across endpoints; however, as we consider primarily relative risk models, and making the reasonable assumption that within a stratum (e.g., defined by cohort, calendar year, age, sex) a fixed proportion of the leukaemia cases would go on to die from that cause, independent of dose (i.e., the lethality does not depend on dose) one would not expect RR/100 mSv to differ appreciably in mortality compared with incidence. The relative risks were somewhat higher in the mortality cohorts than in the incidence cohorts, but the risks did not differ significantly in the two groups of cohorts (Web-appendix p. 24), therefore confirming the reasonableness of the relative risk model and these other assumptions.

It is perhaps notable that there is little evidence in the present study for departure from linearity (i.e., with excess risk proportional to dose) in the leukaemia dose-response (Web-appendix p. 13), suggesting that over the dose range considered a linear dose response is appropriate. For this reason, we mostly modelled leukaemia risk using a simple linear relative risk model, a model that is commonly used in analysis of radio-epidemiological data¹. The linearity is likely to be a reflection of the restriction of attention to the low-dose region (<100 mSv), in which dose-response curvature, based on what has been observed elsewhere (e.g., for acute myeloid leukaemia in the LSS¹⁴), would not be expected. The restriction of mean cumulative ABM doses to <100 mSv, and the consequent reduction in power of the main radiation effect, might reduce our ability to detect any modifying effects, so it is not particularly surprising that we found little evidence of an influence of time since exposure (Web-appendix pp. 14–15), age at exposure (Web-appendix pp. 16–17) or duration of exposure (Web-appendix p. 18).

There was, however, information on latency. The main analyses were conducted with an *a priori* chosen cumulative dose lag of 2 years, implicitly adopting the conventional assumption that the dose received within 2 years of leukaemia diagnosis/death does not affect risk¹. A sensitivity analysis using dose lags of 0, 5 and 10 years showed that a minimum latent period of 2 years was broadly supported and that doses received 2–5 years before diagnosis/death were particularly influential, especially for acute lymphoblastic leukaemia (Web-appendix p. 20). There were also indications ($p \approx 0.05$) of excess acute myeloid leukaemia within 2 years of exposure (Web-appendix p. 19). This illustrates the importance of the eight medically-exposed cohorts in this study: quantitative information on latency under 5 years cannot be derived from the LSS because the follow-up only commenced 5 years after the Japanese atomic bombings (although there was clear evidence of an earlier excess of leukaemia among the survivors before the establishment of the LSS cohort based on clinical reports³²).

With regard to limitations, the potential effects of selection and survival bias should also be considered. Neither the process by which we chose the nine cohorts for study nor the limitation within each cohort to those receiving doses <100 mSv should have introduced bias. The subjects in some cohorts had to survive until start of follow-up (e.g., Canadian TB, LSS, Swedish haemangioma), and in some instances to be eligible for inclusion they had existing medical conditions (e.g., TB, haemangioma, scoliosis) or suspected diseases (UK-NCI CT study). There has been concern about possible survival or selection bias in the LSS data, although the magnitude of any effect of such bias in relation to leukaemia appears to be modest³³. There has also been concern about reverse causation and confounding by indication in the UK-NCI CT study, although for leukaemia with a 2-year dose lag there appears to be little evidence for the former³, and analysis excluding those with underlying medical conditions or pre-existing cancer had little effect on CT-associated leukaemia risk³⁴. Adjustment for socioeconomic status hardly affected either leukaemia baseline risk or associated radiation risk in the UK-NCI CT study³, a finding paralleled in other radiation-exposed groups²⁵. We collected a relatively limited set of variables for each cohort, so it is possible that confounding by some unmeasured factor could bias our results. However, the cohorts included in our analysis were characterised by few major known risk factors for leukaemia other than radiation^{1,35}, and thus, we posit that confounding is unlikely. The

broad consistency of the findings across the different cohorts (Web-appendix pp. 21–23) also suggests that any shortcomings in the component cohorts, in particular biases and unmeasured confounding factors, did not impact materially on the findings of this study.

Dose error is also possible in all dose estimates that we used (Web-appendix pp. 2–3, 5). There are two main types of dose error, classical dose error, which if unadjusted would be expected to bias results towards the null³⁶, and Berkson error which would not be expected to introduce bias, although it might increase the variance of estimated trends with dose³⁶. Therefore, in neither case would one expect such errors to introduce spurious trends with dose. In some cohorts, in particular the LSS, there has been validation of dosimetry via biological markers of exposure¹⁸.

The strengths of the present study are the prospective designs used in all component cohorts, individual ABM dose estimates, relative homogeneity of risk between cohorts (Web-appendix pp. 21–24, 26), as well as the generally long follow-up periods producing a large number of cases exposed at low doses.

There are radiobiological data supportive of a leukaemia risk following low dose exposure. A number of studies have suggested an increase in stable chromosome aberrations and other markers of biological damage in peripheral blood lymphocytes (PBL) of nuclear workers and other groups with protracted radiation exposures, of a magnitude comparable with that seen in the LSS (reviewed in Little *et al*³⁷). Such increases in chromosome aberrations have also been observed after very low dose irradiation of human PBL exposed *ex vivo*³⁸. Furthermore, there is increasing evidence that chromosome changes play a major role in carcinogenesis, in particular leukaemia, reviewed elsewhere³⁹, and that the presence of increased frequencies of chromosome aberrations in PBL in healthy individuals can be considered as surrogate markers for specific changes associated with carcinogenesis, and therefore be indicative of risk³⁹. Indeed, fusion genes generated by chromosomal translocations have long been known to be consistent with genetic abnormalities in paediatric and some adult leukaemias⁴⁰; in particular the *BCR-ABL* translocation, which accounts for almost all cases of chronic myeloid leukaemia⁴⁰.

In summary, we have documented radiogenic excess risks at mean cumulative ABM doses <100 mSv for acute myeloid leukaemia (with or without myelodysplastic syndromes) and acute lymphoblastic leukaemia. The relative risks are somewhat higher than, but compatible with, those seen in other studies with cumulative doses and dose rates both higher and lower than those studied here (Web-appendix p. 27). These findings suggest that there is risk of leukaemia associated with low-level exposure to radiation. As most exposures to workers and the general public stem from low doses⁶, the present study, among others, suggests that the current system of radiological protection is prudent and not overly protective. The findings of the present study also add weight to efforts already underway (<https://www.imagegently.org/>) to minimise diagnostic radiological imaging, particularly in children, wherever possible. Continuing follow-up of these cohorts using up-to-date WHO disease classification combined with a comprehensive and consistent re-evaluation of dosimetry will be valuable and informative.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

FULL ACKNOWLEDGMENTS

The authors are grateful for the detailed and helpful comments of the six referees. This research was funded by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics, National Cancer Institute, US National Institutes of Health; the Radiation Effects Research Foundation (Research Protocol A1–16), Hiroshima and Nagasaki, Japan, jointly supported by the Japanese Ministry of Health, Labour and Welfare and the US Department of Energy (DOE); and through DOE award-DE-HS0000031 to the National Academy of Sciences. The views of the authors do not necessarily reflect those of the US and Japanese governments. LBZ was supported by National Cancer Institute/NIH awards R03CA188614+R01CA197422. MSP is affiliated with the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Chemical and Radiation Threats and Hazards at Newcastle University in partnership with Public Health England (PHE). The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR, the Department of Health or PHE.

Funding National Cancer Institute Intramural Research Program and National Cancer Institute/NIH awards R03CA188614+R01CA197422.

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RESEARCH IN CONTEXT

Evidence before this study

Leukaemia has long been known to be among the most radiosensitive malignancies, and leukaemia generally appears sooner than any other cancer after radiation exposure. At moderate-to-high doses (>0.5 Sv) there is abundant evidence of radiation-related excess risk for most major leukaemia subtypes. Particularly high excess relative risks of leukaemia have been reported following radiation exposure in childhood. However, evidence of risk at lower doses is less well established, in particular at radiation doses of less than 100 mSv, the level of dose often used to demarcate low doses. We conducted PubMed searches at a number of points, and in final form on 29th May 2018 using the terms “leukaemia” + “radiation” + “medical” + “diagnosis”, “leukaemia” + “radiation” + “medical” + “therapy”. We did not limit the language of publication. We also searched comprehensive overviews of the literature prepared by UNSCEAR (2008, 2013) and BEIR VII (2006). We chose all available cohort studies reporting on or before 30th June 2014 and with adequate dosimetry, with 5 leukaemias or myeloid malignancies receiving mean cumulative active bone marrow radiation doses >0.005 Sv while aged <21 years, but excluded any studies of patients being treated for malignant disease, in which chemotherapy is potentially a strong confounder.

Added value of this study

Although there have been previous pooled analyses of leukaemia, this study is the first to provide quantitative assessments of risk for exposures during childhood and adolescence of less than 100 mSv. In a pooled analysis of 9 cohorts with 262,573 subjects exposed at a young age to mean cumulative active bone marrow doses less than 100 mSv we demonstrated highly significant excess risks of acute myeloid leukaemia and acute lymphoblastic leukaemia. Excess risk was also observed for doses under 50 mSv for some endpoints. Exposures 2–5 years before diagnosis/death particularly influenced excess risk, with some indications of risk for exposures within 2 years of diagnosis. There were few indications of non-linearity in dose response, or inter-cohort heterogeneity, in particular between the medically-exposed groups and the Japanese atomic bomb survivors.

Implications of all the available evidence

The radiation risks in this study are somewhat higher than, but compatible with, those seen in other studies, with cumulative doses and dose rates both higher and lower than those studied here. The totality of these studies suggests that there is risk of leukaemia associated with low-level exposure to radiation. As most exposures to workers and the general public stem from low doses, the present study, among others, suggests that the current system of radiological protection is prudent and not overly protective. The findings of the present study also add weight to efforts already underway (<https://www.imagegently.org/>) to minimise diagnostic radiological imaging, particularly in children, wherever possible.

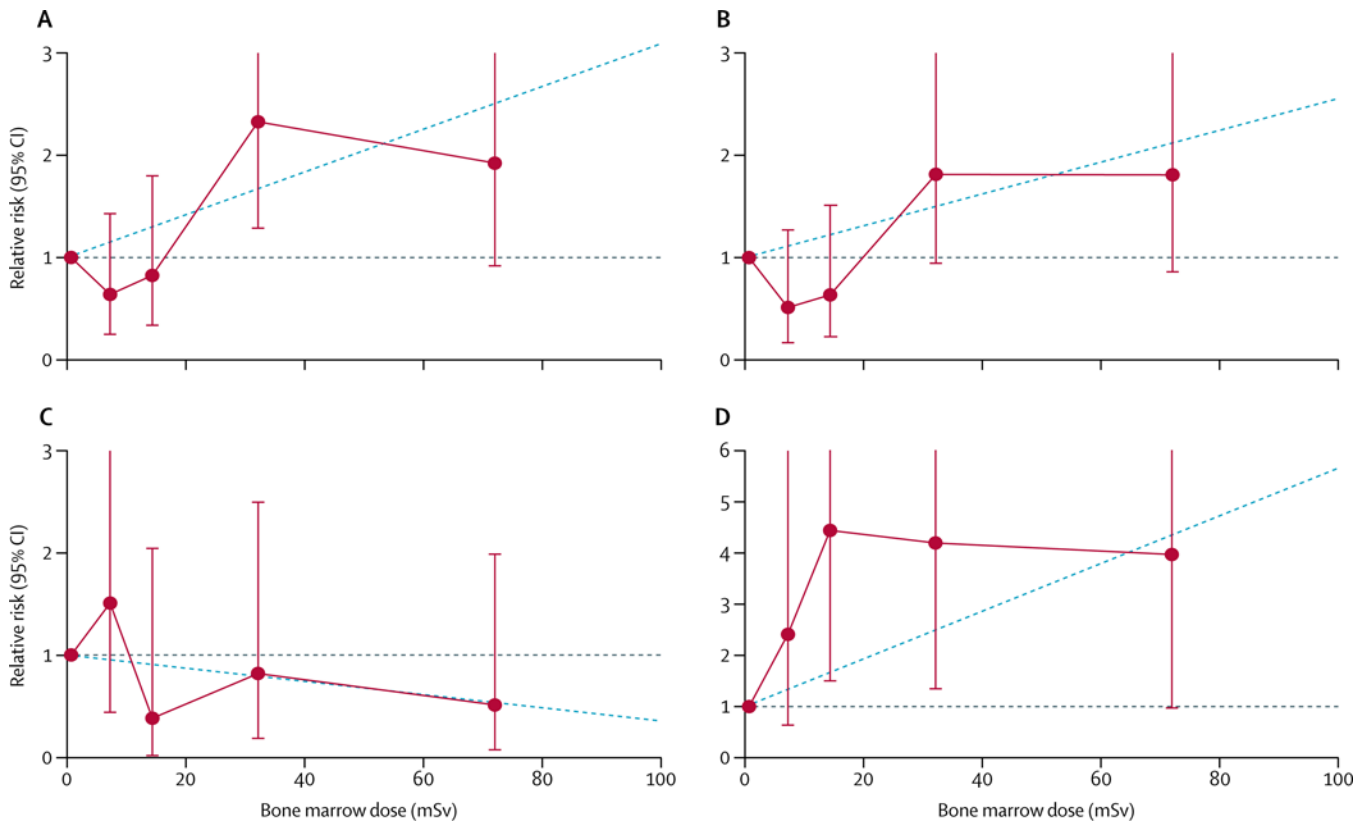


Figure 1. Relative risk (and 95% CI) by mean cumulative active bone marrow radiation doses for (a) acute myeloid leukaemia and myelodysplastic syndromes (MDS), (b) acute myeloid leukaemia, (c) chronic myeloid leukaemia, and (d) acute lymphoblastic leukaemia. Solid red line gives relative risk = 1, dashed green line the fitted linear relative risk model, with RR at 100 mSv taken from Table 2. Dose boundaries used for categories are 0, 5, 10, 20, 100 mSv.

Summary data for persons in nine paediatrically-exposed cohorts with mean cumulative whole-body active bone marrow radiation doses 100 mSv.

Table 1.

Class	Category	Person years	Persons first at risk	Myeloid malignant neoplasms	Acute myeloid leukaemia + myelo-dysplastic syndrome	Acute myeloid leukaemia	Chronic myeloid leukaemia	Acute lympho-blastic leukaemia	Acute leukaemia	Leukaemia excluding chronic lymphocytic leukaemia	Leukaemia
Total		5,154,464	262,573	154	87	79	36	40	139	221	248
Sex	male	2,224,910	132,706	82	49	46	17	19	73	118	130
	female	2,927,350	129,645	72	38	33	19	20	65	102	117
	unknown	2,204	222	0	0	0	0	1	1	1	1
	<1920	56	2	0	0	0	0	0	0	0	0
	1920–1929	37,264	576	2	1	1	1	0	3	4	4
	1930–1939	161,551	4093	10	1	1	3	0	1	13	16
	1940–1949	133,649	4184	3	0	0	2	1	1	14	17
	1950–1959	2,737,850	72,645	90	56	56	22	12	81	121	140
Entry year (calendar year of start of follow-up)	1960–1969	250,198	5732	3	2	2	1	0	2	6	6
	1970–1979	223,412	7777	3	3	2	0	1	7	9	11
	1980–1989	49,542	2700	1	1	1	0	2	3	3	3
	1990–1999	1,049,670	83,988	31	16	10	6	16	26	34	34
	2000	511,275	80,876	11	7	6	1	8	15	17	17
	<1920	4	2	0	0	0	0	0	0	0	0
	1920–1929	1,625	576	0	0	0	0	0	0	0	0
	1930–1939	21,927	4,093	1	0	0	0	0	0	0	0
	1940–1949	52,135	4,184	2	0	0	1	0	0	1	1
	1950–1959	546,001	72,645	9	4	4	3	0	8	21	21
Calendar year of follow-up	1960–1969	673,594	5,732	11	5	5	3	1	12	22	24
	1970–1979	676,721	7,777	14	10	10	3	3	17	22	23
	1980–1989	682,128	2,700	24	13	13	7	5	19	35	36
	1990–1999	909,478	83,988	32	18	17	12	8	28	47	56
	2000–2009	1,542,880	80,876	58	34	27	7	23	52	66	78
	2010	47,977	0	3	3	3	0	0	3	4	6

Class	Category	Person years	Persons first at risk	Myeloid malignant neoplasms	Acute myeloid leukaemia + myelodysplastic syndrome	Acute myeloid leukaemia	Chronic myeloid leukaemia	Acute lymphoblastic leukaemia	Acute leukaemia	Leukaemia excluding chronic lymphocytic leukaemia	Leukaemia
	0-4	775,339	46,045	10	9	7	0	15	25	29	29
	5-9	997,175	42,872	25	14	14	6	10	25	34	38
	10-14	1,038,600	49,060	32	17	13	11	4	23	37	41
Age at entry (years)	15-19	997,089	59,309	36	21	20	9	3	25	38	41
	20-29	1,132,410	56,081	39	23	22	7	7	33	53	64
	30-39	147,594	4973	4	2	2	1	1	6	13	16
	40-49	41,721	1969	4	1	1	1	0	2	10	11
	50	24,534	2264	4	0	0	1	0	0	7	8
	<0 or NA	787,926	34,069	28	8	8	9	3	16	54	60
	0-0.99	12,484	9125	0	0	0	0	0	0	0	0
	1-1.99	14,311	2159	0	0	0	0	0	0	0	0
Years since first exposure	2-4.99	521,372	164,566	8	5	4	2	10	16	20	20
	5-9.99	917,723	44,511	20	11	10	3	11	23	28	28
	10-14.99	595,744	4232	14	8	4	2	5	10	14	14
	15-19.99	373,356	1619	11	8	7	2	0	8	12	12
	20-29.99	555,655	1757	13	8	8	4	4	15	20	20
	30	1,375,890	535	60	39	38	14	7	51	73	94
	0-4.99	101,297	46,045	1	1	1	0	4	6	6	6
	5-9.99	301,866	42,872	1	1	1	0	9	11	13	13
	10-14.99	444,398	49,060	6	4	3	1	9	13	14	14
Attained age (years)	15-19.99	573,247	59,309	17	10	8	3	2	13	17	17
	20-29.99	1,276,510	56,081	27	16	12	7	3	19	30	30
	30-39.99	810,511	4973	15	7	7	5	3	10	19	19
	40-49.99	688,734	1969	19	11	11	5	3	18	27	29
	50	957,904	2264	68	37	36	15	7	49	95	120
Mean cumulative active bone marrow dose (mSv)	0-4.99	2,895,460	131,872	89	41	41	25	7	61	124	142
	5-9.99	613,757	50,610	14	7	5	5	5	12	20	21
	10-19.99	651,922	48,056	11	8	6	1	16	23	26	27

Class	Category	Person years	Persons first at risk	Myeloid malignant neoplasms	Acute myeloid leukaemia + myelo-dysplastic syndrome	Acute myeloid leukaemia	Chronic myeloid leukaemia	Acute lympho-blastic leukaemia	Acute leukaemia	Leukaemia excluding chronic lymphocytic leukaemia	Leukaemia
20-49.99		567,610	22,015	24	19	15	3	8	24	29	34
50-100		425,720	10,020	16	12	12	2	4	19	22	24

Table 2.

Relative risk at 100 mSv (and 95% CI) derived from fitting a linear relative risk model (expression (C1), see Web-appendix p.28) restricted to data in nine paediatrically-exposed cohorts with mean cumulative active bone marrow (ABM) radiation doses ≤ 100 mSv^a

Endpoint	Mean ABM dose group (mSv)	Cases / deaths	Person years	Relative risk, RR (95% CI)	p-value
All myeloid malignant neoplasms (including acute myeloid leukaemia, chronic myeloid leukaemia, other myeloproliferative cancers and myelodysplastic syndromes)	0–4.99	89	2,895,460	1 (=reference)	
	5–9.99	14	613,757	0.69 (0.36, 1.25)	
	10–19.99	11	651,922	0.64 (0.31, 1.23)	
	20–49.99	24	567,610	1.61 (0.98, 2.55)	
	50–100	16	425,720	1.28 (0.69, 2.25)	
	RR at 100 mSv	154	5,154,464	1.75 (0.81, 3.20)	0.136
Acute myeloid leukaemia + myelodysplastic syndromes	0–4.99	41	2,895,460	1 (=reference)	
	5–9.99	7	613,757	0.64 (0.25, 1.43)	
	10–19.99	8	651,922	0.83 (0.34, 1.80)	
	20–49.99	19	567,610	2.33 (1.29, 4.06)	
	50–100	12	425,720	1.92 (0.92, 3.74)	
	RR at 100 mSv	87	5,154,464	3.09 (1.41, 5.92)	0.008
Acute myeloid leukaemia	0–4.99	41	2,895,460	1 (=reference)	
	5–9.99	5	613,757	0.51 (0.17, 1.27)	
	10–19.99	6	651,922	0.64 (0.23, 1.51)	
	20–49.99	15	567,610	1.81 (0.95, 3.30)	
	50–100	12	425,720	1.81 (0.86, 3.53)	
	RR at 100 mSv	79	5,154,464	2.56 (1.09, 5.06)	0.033
Chronic myeloid leukaemia	0–4.99	25	2,895,460	1 (=reference)	
	5–9.99	5	613,757	1.51 (0.44, 4.32)	
	10–19.99	1	651,922	0.38 (0.02, 2.04)	
	20–49.99	3	567,610	0.82 (0.19, 2.49)	
	50–100	2	425,720	0.51 (0.08, 1.98)	
	RR at 100 mSv	36	5,154,464	0.36 (0.00 ^{bc} , 2.36)	0.394
Acute lymphoblastic leukaemia	0–4.99	7	2,895,460	1 (=reference)	
	5–9.99	5	613,757	2.41 (0.64, 8.65)	
	10–19.99	16	651,922	4.45 (1.50, 14.08)	
	20–49.99	8	567,610	4.20 (1.35, 13.28)	
	50–100	4	425,720	3.97 (0.97, 14.15)	
	RR at 100 mSv	40	5,154,464	5.66 (1.35, 19.71)	0.023
Acute leukaemia	0–4.99	61	2,895,460	1 (=reference)	
	5–9.99	12	613,757	0.89 (0.43, 1.71)	
	10–19.99	23	651,922	1.29 (0.71, 2.28)	
	20–49.99	24	567,610	1.82 (1.08, 3.00)	
	50–100	19	425,720	1.98 (1.10, 3.40)	

Endpoint	Mean ABM dose group (mSv)	Cases / deaths	Person years	Relative risk, RR (95% CI)	p-value
Leukaemia excluding chronic lymphocytic leukaemia	RR at 100 mSv	139	5,154,464	2.70 (1.40, 4.71)	0.005
	0–4.99	124	2,895,460	1 (=reference)	
	5–9.99	20	613,757	1.07 (0.62, 1.79)	
	10–19.99	26	651,922	1.14 (0.67, 1.89)	
	20–49.99	29	567,610	1.54 (0.98, 2.36)	
	50–100	22	425,720	1.47 (0.87, 2.36)	
	RR at 100 mSv	221	5,154,464	1.84 (0.97, 3.08)	0.059

^aModels stratified by cohort, sex, age and year of follow-up (using intervals of age and year of follow-up defined by person-year table, as in Web-appendix p. 10). Unless otherwise stated, all confidence intervals are based on the profile likelihood.

^bWald-based CI.

^cpredicted RR = $1+0.1\alpha < 0$ so RR set to 0.

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Table 3.

Relative risk (RR) at 100 mSv (and 95% CI) for follow-up restricted to mean cumulative active bone marrow (ABM) doses of <100 mSv, <50 mSv and <20 mSv^a

	RR at 100 mSv (+95% CI)	Cases/deaths	p-value
Mean cumulative ABM doses < 100 mSv			
Acute myeloid leukaemia + myelodysplastic syndromes	3.09 (1.41, 5.92)	87	0.008
Acute myeloid leukaemia	2.56 (1.09, 5.06)	79	0.033
Chronic myeloid leukaemia	0.36 (0.0 ^c , 2.36)	36	0.394
Acute lymphoblastic leukaemia	5.66 (1.35, 19.71)	40	0.023
Mean cumulative ABM doses < 50 mSv			
Acute myeloid leukaemia + myelodysplastic syndromes	4.88 (1.79, 10.17)	75	0.007
Acute myeloid leukaemia	3.41 (0.81, 7.95)	67	0.076
Chronic myeloid leukaemia	0.63 ^b (0.0 ^{cd} , 5.81)	34	0.825 ^b
Acute lymphoblastic leukaemia	11.52 (1.99, 45.45)	36	0.016
Mean cumulative ABM doses < 20 mSv			
Acute myeloid leukaemia + myelodysplastic syndromes	0.53 ^b (0.0, 8.95)	56	0.872 ^b
Acute myeloid leukaemia	0.0 ^d (0.0 ^{cd} , 5.90)	52	0.423
Chronic myeloid leukaemia	0.0 ^d (0.0 ^{cd} , 9.46)	31	0.357
Acute lymphoblastic leukaemia	45.09 (7.86, 192.50)	28	0.003

^aModels stratified by cohort, sex, age and year of follow-up (using intervals of age and year of follow-up defined by person-year table, as in Web-appendix p. 10). Unless otherwise stated, all confidence intervals are based on the profile likelihood.

^bindications of lack of convergence.

^cWald-based confidence limit.

^dpredicted RR = 1+0.1 α < 0 so RR set to 0.