Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study

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Summary

Background There is much uncertainty about the risks of leukaemia and lymphoma after repeated or protracted low-dose radiation exposure typical of occupational, environmental, and diagnostic medical settings. We quantified associations between protracted low-dose radiation exposures and leukaemia, lymphoma, and multiple myeloma mortality among radiation-monitored adults employed in France, the UK, and the USA.

Methods We assembled a cohort of 308 297 radiation-monitored workers employed for at least 1 year by the Atomic Energy Commission, AREVA Nuclear Cycle, or the National Electricity Company in France, the Departments of Energy and Defence in the USA, and nuclear industry employers included in the National Registry for Radiation Workers in the UK. The cohort was followed up for a total of 8·22 million person-years. We ascertained deaths caused by leukaemia, lymphoma, and multiple myeloma. We used Poisson regression to quantify associations between estimated red bone marrow absorbed dose and leukaemia and lymphoma mortality.

Findings Doses were accrued at very low rates (mean 1·1 mGy per year, SD 2·6). The excess relative risk of leukaemia mortality (excluding chronic lymphocytic leukaemia) was 2·96 per Gy (90% CI 1·17–5·21; lagged 2 years), most notably because of an association between radiation dose and mortality from chronic myeloid leukaemia (excess relative risk per Gy 10·45, 90% CI 4·48–19·65).

Interpretation This study provides strong evidence of positive associations between protracted low-dose radiation exposure and leukaemia.

Funding Centers for Disease Control and Prevention, Ministry of Health, Labour and Welfare of Japan, Institut de Radioprotection et de Sûreté Nucléaire, AREVA, Electricité de France, National Institute for Occupational Safety and Health, US Department of Energy, US Department of Health and Human Services, University of North Carolina, Public Health England.

Introduction

Although exposure to high-dose ionising radiation is rare outside of radiotherapy, repeated or protracted low-dose exposure has become increasingly common over the past 25 years.[1] Occupational and environmental sources of radiation exposure are important; however, the largest contributor to this trend is medical radiation exposure. In 1982, the average yearly dose of ionising radiation from medical exposures was about 0·5 mGy per person in the USA; by 2006, it had increased to 3·0 mGy.[2] A similar pattern exists in other high-income countries: use of diagnostic procedures involving radiation in the UK more than doubled over that period[3] and more than tripled in Australia.[4] Because ionising radiation is a carcinogen,[5] its use in medical practice must be balanced against the risks associated with patient exposure.[6]

The primary basis for estimating cancer risks from ionising radiation exposures are epidemiological studies of Japanese survivors of the atomic bombings of Hiroshima and Nagasaki in August, 1945.[7] Within a few years of the bombings there was evidence of an excess of leukaemia, predominantly myeloid subtypes, among survivors.[8–12] These findings helped to establish that ionising radiation causes leukaemia.[13] However, this evidence mostly relates to acute high-dose exposure. The risks associated with protracted or repeated low-dose exposures are more relevant to the public and health practitioners.

The International Nuclear WORKers Study (INWORKS) was done to strengthen the scientific basis for protecting people from low-dose protracted or intermittent radiation exposure. It included workers from France,[14] the UK,[15] and the USA[16] who have been monitored for external exposure to radiation with personal dosimeters and followed up for up to 60 years after exposure. Here, we report data for leukaemia, lymphoma, and multiple myeloma mortality among participants of INWORKS.

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Research in context

Evidence before this study

Ionising radiation causes leukaemia. The primary quantitative basis for radiation protection standards comes from studies of populations exposed to acute, high doses of ionising radiation. Although previous studies of nuclear workers addressed leukaemia radiogenicity, questions remain about the size of the risk from protracted radiation exposure in occupational settings.

Added value of this study

We report a positive dose–response relationship between cumulative, external, protracted, low-dose exposure to ionising radiation, and subsequent death caused by leukeamia (excluding chronic lymphocytic leukaemia). The risk coefficient per unit dose was consistent with those derived from analyses of other populations exposed to higher radiation doses and dose rates.

Implications of all the available evidence

The present study provides strong evidence of a positive association between radiation exposure and leukaemia even for low-dose exposure. This finding shows the importance of adherence to the basic principles of radiation protection—to optimise protection to reduce exposures as much as reasonably achievable and—in the case of patient exposure—to justify that the exposure does more good than harm.

Methods

Study design and participants

The INWORKS cohort consists of nuclear workers from three of the major partners included in the previously published 15-country study of cancer among workers in the nuclear industry:[17] France,[14] the UK,[15] and the USA.[16] Less than 20% of deaths from leukaemia were contributed by the other 12 countries.[18] These cohorts have been updated since the 15-country study. INWORKS includes fewer partners than the earlier 15-country study because of the limited resources and the consequent need for efficiency in project coordination.

The study includes workers employed by the French Atomic Energy Commission, AREVA Nuclear Cycle, and Electricité de France, workers employed by the British Atomic Weapons Establishment, British Nuclear Fuels, the UK Atomic Energy Authority, British Energy Generation, the UK Ministry of Defence, and other organisations providing data to the National Registry for Radiation Workers, and workers employed by the US Department of Energy's Hanford Site, Savannah River Site, Oak Ridge National Laboratory, Idaho National Laboratory, and the Portsmouth Naval Shipyard. Workers who were employed in the nuclear industry for less than 1 year were excluded. In France, workers were given the opportunity to refuse participation, which is required by the French Data Protection Authority; however, none did. In the USA, worker information was taken from existing records, with no direct contact with any participants; because there is minimal risk to participants, the National Institute for Occupational Safety and Health institutional review board waived requirements for informed consent. UK workers can refuse to participate in the National Registry for Radiation Workers and associated studies; less than 1% did.

Procedures

Participants were followed up for a total of 8·22 million person-years to ascertain vital status up to 2004 in France, 2001 in the UK, and 2005 in the USA. Underlying cause of death was abstracted from death certificates and generally coded according to the revision of the International Classification of Diseases (ICD) in effect at the time of death. We assessed leukaemia other than chronic lymphocytic leukaemia (CLL; ICD9 codes 204–208 excluding 204.1 and 204.9), acute myeloid leukaemia (ICD9 codes 205.0, 206.0, 207.0, and 207.2), chronic myeloid leukaemia (ICD9 code 205.1), acute lymphoblastic leukaemia (ICD9 code 204.0), and CLL (ICD9 code 204.1). We assessed lymphoma deaths separately for non-Hodgkin lymphoma (ICD9 codes 200, 202, 273.3), Hodgkin's lymphoma (ICD9 code 201), and multiple myeloma (ICD9 code 203). The appendix (p 2) shows an exhaustive list of ICD codes.

Data for monitoring exposure to ionising radiation were available from dose registry, government, and company records, providing individual yearly estimates of whole-body exposure to external penetrating radiation (primarily γ rays). Red bone marrow absorbed doses expressed in Gy were derived by dividing recorded external penetrating radiation dose estimates by the appropriate organ dose conversion factor.[19,20] In this report, dose indicates absorbed dose to red bone marrow expressed in Gy. Because most external exposures were to high-energy photons, with a radiation weighting factor of 1·0, absorbed dose in Gy could be expressed in terms of equivalent dose in Sieverts.

Statistical analysis

Participants entered the study either 1 year after the date of first employment or on the date of first dosimetric monitoring, whichever was later. In France, the national death registry recorded information on individual causes of death only since 1968; therefore, French workers entered follow-up on Jan 1, 1968, or later. Participants remained in the study until the earliest of date of death, date lost to follow-up, or end of follow-up. We estimated relative risk (RR) by a model of the form $RR = 1 + \beta d$, generally used in studies of radiation effects,[21] where d is the dose and β is an estimate of the excess relative risk (ERR; $RR-1$) per unit dose; we derived likelihood-based CIs. All models were stratified by country, sex, calendar period (<1946, 1946–50...

1996–2000, ≥2001), and age (<35, 35–39…70–74, ≥75); these potential confounders were selected a priori from a set of measured covariates. We also fitted linear-quadratic and pure-quadratic functions of dose and selected a model with Akaike information criterion.[22]

To allow for an induction and latency period between exposure to radiation and death, cumulative doses were lagged by 2 years for analyses of leukaemia mortality and by 10 years for analyses of lymphoma and multiple myeloma. These lag assumptions were chosen a priori. In sensitivity analyses we assessed a 10-year lag for analyses of leukaemia mortality and a 2-year lag for analyses of lymphoma and multiple myeloma, fitted models to restricted ranges of dose, and excluded workers with substantial doses from neutrons (ie, workers with recorded cumulative neutron doses exceeding 10% of the total equivalent dose for external radiation). To provide empirical support for the absence of confounding by socioeconomic status, we report supplementary analyses adjusted for socioeconomic status (based on job title: managers and engineers, administrative staff, skilled workers, unskilled workers, uncertain); and, to address concern about potential confounding by internal contamination, we report analyses adjusted for known or suspected internal radiation exposure. We did the analyses excluding one country at a time to assess the effect of a single country on overall results. Because the objective of most contemporary radiation epidemiological studies is to investigate the potential for an increased cancer risk in relation to radiation exposure, one-sided p values and corresponding 90% CIs are usually presented; we follow that convention here by reporting 90% CIs. All models were fitted with EPICURE software.[23]

Role of the funding source

The funders had no role in study design, data analysis, data interpretation, or writing of the report. AREVA and Électricité de France provided historical occupational data and individual monitoring data for part of the French cohort. KL, DBR, and MM had full access to all the data in the study. KL and DBR had final responsibility for the decision to submit for publication.

Results

We assembled a cohort of 308 297 radiation-monitored workers. Table 1 shows the characteristics of the study population. Mean follow-up was 27 years (SD 12) and nearly 22% of the workers were deceased at the end of follow-up. Mean cumulative dose was 16 mGy. The median was 2·1 mGy (IQR 0·3–11·7), with a tenth percentile of 0·0 mGy and a 90th percentile of 40·8 mGy (appendix p 1). The mean yearly dose was 1·1 mGy (SD 2·6).

We recorded 531 deaths caused by leukaemia excluding CLL, 814 caused by lymphoma, and 293 caused by multiple myeloma. 281 (53%) of 531 deaths caused by leukaemia excluding CLL occurred in people who had accrued less than 5 mGy (appendix p 3). The RR of death caused by

	France	USA	UK	Overall
Study period	1968–2004	1944–2005	1946–2001	1944–2005
Number of participants	59 003	101 428	147 866	308 297
Person-years (millions)	1·47	3·34	3·41	8·22
Duration of follow-up (years)				
Mean (SD)	25 (9)	33 (13)	23 (12)	27 (12)
Median (IQR)	23 (18–36)	31 (23–44)	22 (14–32)	26 (18–36)
Age at last observation (years)				
Mean (SD)	56 (13)	65 (13)	54 (15)	58 (15)
Median (IQR)	54 (46–66)	66 (55–76)	54 (42–66)	58 (47–70)
Sex				
Male	51 567 (87%)	81 883 (81%)	134 812 (91%)	268 262 (87%)
Female	7436 (13%)	19 545 (19%)	13 054 (9%)	40 035 (13%)
Vital status on Dec 31, 2005				
Alive	52 565 (89%)	65 573 (65%)	118 775 (80%)	236 913 (77%)
Died	6310 (11%)	35 015 (35%)	25 307 (17%)	66 632 (22%)
Number of deaths from malignant neoplasm of lymphoid and haemopoietic tissues (% of total deaths)	196 (3%)	1031 (3%)	564 (2%)	1791 (3%)
Emigrated or lost to follow-up	128 (<1%)	840 (1%)	3784 (3%)	4752 (2%)
Cumulative red bone marrow dose (mGy)				
Mean (range)	11·6 (0·0–415·8)	15·2 (0·0–820·2)	18·2 (0·0–1217·5)	15·9 (0·0–1217·5)
Median (IQR)	1·3 (0·0–10·7)	1·9 (0·2–10·6)	2·6 (0·4–12·9)	2·1 (0·3–11·7)

Data are n (%) unless stated otherwise.

Table 1: Characteristics of individuals included in INWORKS

leukaemia excluding CLL by categories of cumulative dose showed a substantial risk for cumulative dose above 200 mGy (appendix p 3). The estimated ERR of mortality caused by leukaemia excluding CLL was 2·96 per Gy (90% CI 1·17–5·21; table 2). The trend in the ERR of leukaemia excluding CLL with dose was well described by a simple linear function of cumulative dose; inclusion of a higher order polynomial function (ie, a linear-quadratic or pure-quadratic function of dose) did not substantially improve the model fit (the Akaike information criterion was lowest for the pure-quadratic model but only differed by 0·3 from that of the linear model; data not shown). The ERR of leukaemia excluding CLL was not attenuated when restricted to doses of less than 300 mGy or less than 100 mGy (figure); however, 90% CIs were much wider when based on data for the restricted dose range.

We assessed the associations between cumulative dose and subtypes of leukaemia. We detected positive associations for chronic myeloid leukaemia, acute

myeloid leukaemia, and acute lymphoblastic leukaemia; the association was largest for chronic myeloid leukaemia (table 2). Associations also were positive but highly imprecise for Hodgkin's lymphoma, non-Hodgkin lymphoma, and multiple myeloma with CIs that spanned zero (table 2). The association between radiation dose and CLL mortality was negative (table 2).

Alternative lag assumptions resulted in little change in the ERR per Gy (appendix p 4). When adjusting the ERR model for socioeconomic status, the ERR per Gy was practically unchanged for leukaemia excluding CLL and for chronic myeloid leukaemia (appendix p 5). Similarly, adjustment for internal radiation contamination had little effect (appendix p 5). We assessed the effect of excluding people who had recorded neutron exposures; we showed a positive association for leukaemia excluding CLL (ERR per Gy 4·19, 90% CI 1·42–7·80, 453 deaths) and chronic myeloid leukaemia (ERR per Gy 9·55, 90% CI 2·39–21·7, 79 deaths). To assess whether any single country substantially affected the results, we assessed radiation-mortality associations excluding one country at a time (appendix p 6). The estimated ERR per Gy for leukaemia excluding CLL was 2·95 (90% CI 1·13–5·24) when excluding France, 2·32 (0·03–5·33) when excluding the UK, and 3·68 (1·09–7·29) when excluding the USA (appendix p 6). For multiple myeloma and Hodgkin's lymphoma, the associations could not be estimated when excluding the USA, but the multiple myeloma was positive when excluding the UK (ERR per Gy 3·32 [90% CI 0·27–7·64]).

Discussion

We showed a positive association between cumulative dose of ionising radiation and death caused by leukaemia (excluding CLL) among adults who were typically exposed to low doses. The association was greatest for chronic myeloid leukaemia, with positive but imprecise dose–response for deaths caused by acute myeloid leukaemia, acute lymphoblastic leukaemia, Hodgkin's lymphoma, non-Hodgkin lymphoma, and multiple myeloma.

The estimated association between cumulative radiation dose with a 2-year exposure lag assumption and death caused by leukaemia excluding CLL was similar in size and precision to the linear dose–response estimate for male atomic bomb survivors exposed between the ages of 20 and 60 years (ERR at 1 Sv 2·63, 90% CI 1·50–4·27).[14] Although based on a substantially lower dose distribution than in analyses of atomic bomb survivors, typically with very low doses accrued over a long period, the similar size of the associations supports contemporary estimates of risk of leukaemia after adult exposure to radiation. This is notable because our estimates were not extrapolated from data for acute exposures.

In previous analyses of cancer among workers in 15 countries,[18] the association between mortality for leukaemia excluding CLL and cumulative radiation dose

	Deaths	ERR per Gy	90% CI
Leukaemia excluding CLL*	531	2·96	1·17 to 5·21
Chronic myeloid leukaemia*	100	10·45	4·48 to 19·65
Acute myeloid leukaemia*	254	1·29	–0·82 to 4·28
Acute lymphoblastic leukaemia*	30	5·80	NE to 31·57
CLL*	138	–1·06	NE to 1·81
Multiple myeloma†	293	0·84	–0·96 to 3·33
Non-Hodgkin lymphoma†	710	0·47	–0·76 to 2·03
Hodgkin's lymphoma†	104	2·94	NE to 11·49

ERR estimated with a linear model stratified by country, calendar period, sex, and age. NE lower CI bound could not be estimated because it was on the boundary of the parameter space (–1/maximum dose). 14 deaths were assigned ICD9 code 204.9 (lymphoid leukaemia, unspecified) and one death was assigned ICD9 code 202.9 (other and unspecified malignant neoplasms of lymphoid, haemopoietic, and related tissue) were excluded from the cause-specific analyses. *2-year lagged cumulative dose. †10-year lagged cumulative dose. ERR=excess relative risk. CLL=chronic lymphocytic leukaemia. NE=not estimable.

Table 2: ERR per Gy of cumulative red bone marrow dose for causes of death
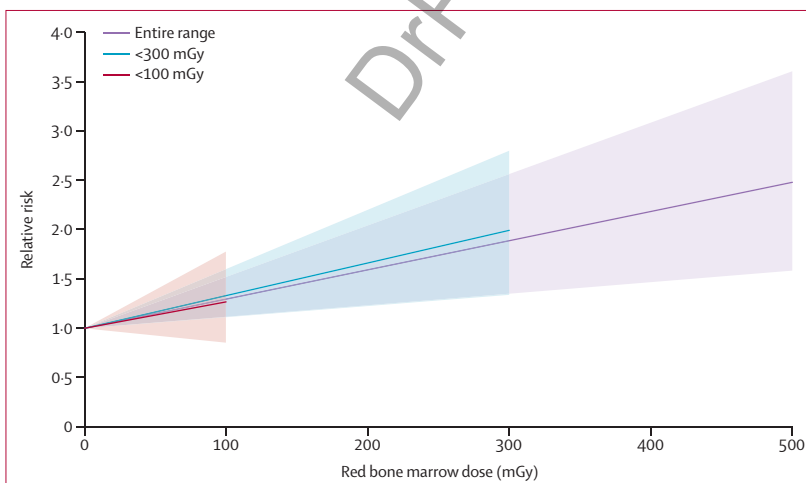

Figure: Relative risk of leukaemia excluding chronic lymphocytic leukaemia associated with 2-year lagged cumulative red bone marrow dose
The lines are the fitted linear dose–response model and the shading represents the 90% CIs.

with a 2-year exposure lag assumption (ERR per Sv 1·93, 90% CI <0–7·14) was smaller and much less precise than the estimate we obtained in our pooled analysis of three countries. The gain in precision is a result of the larger number of deaths from leukaemia excluding CLL in INWORKS (n=531) compared to the earlier study (n=196), because of longer follow-up (mean follow-up in INWORKS was 27 years vs 13 years in the 15-country study[17]) and the enlargement of the French, UK, and US cohorts compared with previous analyses.[14–16] Moreover, the 15-country study excluded people with potential exposures from neutron and internal contamination. In our study, we included 127 deaths caused by leukaemia excluding CLL for workers with potential exposure to neutron and internal contamination. Similarly, the risk estimate for non-Hodgkin lymphoma in the INWORKS study was more precise than the estimate reported in the 15-country study,[24] again because the present study included more deaths (248 in the 15-country study, 710 in the present study). The CIs do not overlap for estimated associations between radiation dose and death caused by acute and chronic myeloid leukaemia; a formal test of heterogeneity in associations by leukaemia subtype would require a joint modelling approach and was not used here.

We did not find any effect of a single country on the estimated association for leukaemia excluding CLL. For multiple myeloma, the association was significantly positive when only the UK data were excluded, suggesting a possible heterogeneity in the risk pattern between the three cohorts. Schubauer-Berigan and colleagues[16] reported a significant increased risk of multiple myeloma mortality associated with dose in their analysis of the USA cohort (ERR per 10 mSv 3·9, 90% CI 0·6–9·6), whereas no significant dose-related excess was detected in the third analysis of the UK National Registry for Radiation Workers (although a significant excess risk was recorded in an analysis of incidence).[15] Multiple myeloma has a potentially long period of development of up to 20 years. The older age at the end of follow-up in the USA cohort might explain the heterogeneity.

We tried to reduce uncertainties in dose estimates that could bias dose–response analyses.[20] Nevertheless, occupational radiation dose estimates are prone to measurement error; consequently, exposure misclassification is an unavoidable study limitation. Outcome misclassification is also a potential concern in studies that rely on death certificates for classification of leukaemia and lymphoma by subtype. This concern is well known for CLL, for which incidence studies seem more appropriate.[25–28] Poor sensitivity and imperfect specificity of death certificates might reduce statistical precision and induce bias in analyses of subtypes. However, death certificate information remains a valuable resource for this type of cohort investigation.

There are few potential confounders of the associations under study. For example, smoking causes myeloid leukaemia;[29,30] however, the size of this association is relatively small[31] and therefore would require large differences in smoking across levels of cumulative dose to cause substantial confounding of the radiation–leukaemia association. Moreover, adjusting risk analyses by socio-economic status would reduce substantial confounding by smoking.[32] Adjustment for socioeconomic status resulted in little change in the risk estimate for leukaemia excluding CLL. Exposure of nuclear workers to other causes of leukaemia such as benzene[29,30] cannot be excluded as a potential source of bias, even though benzene was not widely used in the nuclear industry. In a previous analysis of US nuclear workers, Schubauer-Berigan and coworkers[33] reported weak evidence of confounding by benzene exposure when analysing leukaemia risk associated with external radiation exposure. Benzene exposure could not be assessed for the INWORKS study. Internal exposures to radionuclides—notably uranium and plutonium—occurred at the study sites, and we did not evaluate doses from these intakes. However, our sensitivity analyses showed that internal contamination might have little effect on the relation between external radiation exposure and leukaemia risk. These results are consistent with the conclusions of Shilnikova and colleagues,[34] who reported no indication of any effect of internal contamination on leukaemia mortality among nuclear workers, whereas the risk of leukaemia was positively associated with external γ-ray exposure.

Medical workers are also exposed to low doses of external γ-rays or x-rays. No study has provided estimates of leukaemia risk for medical workers because accurate historical dosimetry data are not available for these populations.[35] Liu and colleagues[36] estimated mortality in a cohort of 90 268 USA radiological technologists. They reported that the leukaemia risk was doubled for technologists who had worked for more than 30 years compared with those who had worked for less than 10 years, but the cohort did not provide any information about doses received by the workers.

In summary, this study provides strong evidence of an association between protracted low dose radiation exposure and leukaemia mortality. At present, radiation protection systems are based on a model derived from acute exposures, and assumes that the risk of leukaemia per unit dose progressively diminishes at lower doses and dose rates.[37] Our results provide direct estimates of risk per unit of protracted dose in ranges typical of environmental, diagnostic medical, and occupational exposure.

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