Leukaemia, lymphoma, and multiple myeloma mortality after low-level exposure to ionising radiation in nuclear workers (INWORKS): updated findings from an international cohort study

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Summary

Background A major update to the International Nuclear Workers Study (INWORKS) was undertaken to strengthen understanding of associations between low-dose exposure to penetrating forms of ionising radiation and mortality. Here, we report on associations between radiation dose and mortality due to haematological malignancies.

Methods We assembled a cohort of 309 932 radiation-monitored workers (269 487 [87%] males and 40 445 [13%] females) employed for at least 1 year by a nuclear facility in France (60 697 workers), the UK (147 872 workers), and the USA (101 363 workers). Workers were individually monitored for external radiation exposure and followed-up from Jan 1, 1944, to Dec 31, 2016, accruing 10·72 million person-years of follow-up. Radiation-mortality associations were quantified in terms of the excess relative rate (ERR) per Gy of radiation dose to red bone marrow for leukaemia excluding chronic lymphocytic leukaemia (CLL), as well as subtypes of leukaemia, myelodysplastic syndromes, non-Hodgkin and Hodgkin lymphomas, and multiple myeloma. Estimates of association were obtained using Poisson regression methods.

Findings The association between cumulative dose to red bone marrow, lagged 2 years, and leukaemia (excluding CLL) mortality was well described by a linear model (ERR per Gy 2·68, 90% CI 1·13 to 4·55, n=771) and was not modified by neutron exposure, internal contamination monitoring status, or period of hire. Positive associations were also observed for chronic myeloid leukaemia (9·57, 4·00 to 17·91, n=122) and myelodysplastic syndromes alone (3·19, 0·35 to 7·33, n=163) or combined with acute myeloid leukaemia (1·55, 0·05 to 3·42, n=598). No significant association was observed for acute lymphoblastic leukaemia (4·25, –4·19 to 19·32, n=49) or CLL (0·20, –1·81 to 2·21, n=242). A positive association was observed between radiation dose and multiple myeloma (1·62, 0·06 to 3·64, n=527) whereas minimal evidence of association was observed between radiation dose and non-Hodgkin lymphoma (0·27, –0·61 to 1·39, n=1146) or Hodgkin lymphoma (0·60, –3·64 to 4·83, n=122) mortality.

Interpretation This study reports a positive association between protracted low dose exposure to ionising radiation and mortality due to some haematological malignancies. Given the relatively low doses typically accrued by workers in this study (16 mGy average cumulative red bone marrow dose) the radiation attributable absolute risk of leukaemia mortality in this population is low (one excess death in 10 000 workers over a 35-year period). These results can inform radiation protection standards and will provide input for discussions on the radiation protection system.

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For the French translation of the abstract see Online for appendix 1

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Introduction

Within a few years of the atomic bombings of Hiroshima and Nagasaki, an excess of leukaemia, primarily myelogenous, was recognised among the survivors.[1,2] Today, it is well established that many types of leukaemia can be caused by exposure to ionising radiation.[1,3] Quantitative estimates of leukaemia risks from ionising radiation exposures are primarily derived from epidemiological studies of people exposed to acute, high doses of ionising radiation.[2,4] However, many of the questions of most relevance to the public and radiation workers concern the excess risk of leukaemia after repeated or protracted low-dose exposures to ionising radiation, as is typically encountered in contemporary occupational, environmental, and diagnostic medical settings.

The International Nuclear Workers Study (INWORKS) was undertaken to strengthen evidence regarding associations between protracted low-dose, low dose-rate radiation exposure and mortality.[5] INWORKS includes workers from France, the UK, and the USA who were monitored for external exposure to ionising radiation using personal dosimeters, and subsequently followed up to collect

Research in context

Evidence before this study

A formal literature search was not done; rather, we drew upon major reviews of the literature. The primary quantitative basis for radiation protection standards comes from studies of populations exposed to acute, high doses of ionising radiation. We previously showed the feasibility of pooling data for radiation workers from some of the world's most informative cohorts in the UK, France, and the USA. Findings from the INWORKS study contributed to discussions by the organisations that advise on ionizing radiation protection.

Added value of this study

This update of the INWORKS study, with 10·72 million person-years of follow-up, strengthens evidence of positive dose–response relationships between cumulative low-dose external exposure to ionising radiation and death caused by leukaemia (excluding chronic lymphocytic leukaemia), but also myelodysplastic syndromes and multiple myeloma, improving knowledge of the causes of these diseases. The excess risk coefficient per unit dose for leukaemia derived from this study is consistent with values reported from analyses of other populations exposed to radiation at higher doses and higher dose rates, whereas the excess risk coefficient per unit dose for multiple myeloma was larger than values reported in those studies.

Implications of all the available evidence

The updated results of INWORKS shed new light on the radiogenicity of haemopathies such as myelodysplastic syndromes and multiple myeloma, and adds to our knowledge of cancer risks associated with the low-dose exposure patterns that are experienced in many contemporary settings. These findings show 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.

information on vital status and causes of death.[6] In 2023, we published a major update of the INWORKS study, with a workers' follow-up of 35 years on average.[7] Here, we report on associations between ionising radiation and leukaemia excluding chronic lymphocytic leukaemia (CLL), hereinafter non-CLL leukaemia, as well as subtypes of leukaemia, lymphoma, and multiple myeloma mortality using information from this update of INWORKS.

Methods

Study design and participants

INWORKS is an international retrospective cohort study of nuclear workers who were employed in France, the UK, and the USA. The research consortium, led by the International Agency for Research on Cancer, has conducted related mortality investigations since the mid-1990s, carried out using a common core protocol, evaluation of the comparability of recorded dose estimates across facilities and time, and a thorough study of errors in recorded doses to identify and quantify sources of bias and uncertainties in dose estimates.[8] INWORKS is the latest stage of this work, which includes participating countries that have consistently provided the greatest contribution to previous consortium work. In addition, these countries, through periodic country-specific analyses,[9–12] have made continuous improvements to available study data, including extending follow-up.

Details describing the formation of the INWORKS cohort have been described elsewhere.[5] Briefly, participating facilities were those including workers who were primarily exposed to low-linear energy transfer (LET) penetrating radiations from external sources and had records of annual doses from monitoring of external radiation exposure using personal dosimeters. Records were obtained from the French Alternative Energies and Atomic Energy Commission, Orano, and Electricité de France; from the UK National Registry for Radiation Workers (NRRW) which includes information from the British Atomic Weapons Establishment, British Nuclear Fuels, the UK Atomic Energy Authority, British Energy Generation, Magnox Electric, and the UK Ministry of Defence; and from the US Department of Energy's Hanford Site, Savannah River Site, Oak Ridge National Laboratory, and Idaho National Laboratory, as well as from the Portsmouth Naval Shipyard.[5] The inclusion criteria in the INWORKS study were to have been employed for at least 1 year in one of the participating companies and to have been badge-monitored as part of regulatory radiation protection monitoring.

Given the retrospective nature of the study and because there is minimal risk to participants, the French Data Protection Authority and the National Institute for Occupational Safety and Health institutional review board waived requirements for individual informed consent. UK workers can refuse to participate in the National Registry for Radiation Workers and associated studies; less than 1% did. The study was approved by the International Agency for Research on Cancer's ethical review committee (No 11–09 and later amendments) and relevant ethical committees of the participating countries. This study was reviewed and approved by the National Institute for Occupational Safety and Health Institutional Review Boad.

Procedures

Individual quantitative annual estimates of body dose due to external exposure to ionising radiation, primarily photons, were available from company records for UK workers and government and company records for US and French workers. Unless otherwise stated, any reference to dose in this paper implies estimated absorbed dose to red bone marrow expressed in Gy, where bone marrow doses were derived by dividing

recorded external penetrating radiation dose estimates by an organ-specific dose factor.[13] Available records of estimated neutron doses were used to construct categories of time-varying neutron monitoring status: whether a worker had a positive recorded neutron dose, and if so, whether their recorded neutron dose ever exceeded 10% of their total external radiation dose of record.[13] As only a few bioassay results were available for the entire cohort, information on monitoring status and workstation risk potential were also used to identify workers with no risk of internal radionuclide contamination (so-called not monitored) and workers with known or suspected internal contaminations (so-called monitored).[13]

A worker entered the study 1 year after the date of first employment or the date of first dosimetric monitoring, whichever was later. However, because in France the national death registry provides individual information on medical causes of death only since 1968, French workers only entered follow-up on Jan 1, 1968, or later.[6] A worker exited the study on the earliest of the following: date of death, date lost to follow-up, or date of end of follow-up.

Vital status was ascertained until Dec 31, 2012, for the UK cohort, Dec 31, 2014, for the French cohort, and Dec 31, 2016 for the US cohort through linkage with national and regional death registries, employer records, tax records, and Social Security Administration records. Information on underlying causes of death was abstracted from death certificates and generally was coded according to the revision of the ICD in effect at the time of death.[5]

Outcomes

Analyses examine the following mortality outcomes: non-CLL leukaemia (ICD9 codes 204–208 excluding 204.1, 204.9, 208.1, and 208.9), chronic myeloid leukaemia (ICD9 codes 205.1 and 206.1), acute myeloid leukaemia (ICD9 codes 205.0, 205.3, 206.0, 207.0, and 207.2), myelodysplastic syndromes (ICD10 code D46), acute lymphoblastic leukaemia (ICD9 code 204.0), CLL (ICD9 code 204.1), non-Hodgkin lymphoma (ICD9 codes 200, 202, 273.3), Hodgkin lymphoma (ICD9 code 201), and multiple myeloma (ICD9 code 203). An exhaustive list of ICD codes is shown in the supplementary material (appendix 2 p 1). We report on non-CLL leukaemia as it is now recognised that there are clinical and etiological links between CLL and lymphomas and that CLL and small lymphocytic lymphoma are different forms of the same disease.[14]

Statistical analysis

Analyses were conducted using multiway tabulations of person-years at risk and deaths by country, sex, attained age (in 5 year intervals), year of birth (in 10 year intervals), socioeconomic status (French, US, and UK workers employed by the Atomic Energy Authority and Atomic Weapons Establishment were classified into five categories, based on job title: professional and technical workers, administrative staff, skilled workers, unskilled workers, and uncertain [5778 or 2% workers]; other UK workers were classified into two broader categories of non-industrial and industrial employees), duration of employment or radiation work (in 5 year intervals), neutron monitoring status (in three categories: whether a worker had a positive recorded neutron dose, and if so, whether their recorded neutron dose ever exceeded 10% of their total external radiation dose), internal contamination monitoring flag (not monitored *vs* monitored), period of first employment, and cumulative dose (in categories <5, 5<10, 10<20, 20<50, 50<100, 100<200, 200<300, and ≥300 mGy). For each cell of this table, the person-time weighted cell-specific mean doses to red bone marrow were calculated. The distribution of person-years by country, birth cohort or attained age, and sex in INWORKS is presented in appendix 2 (p 2).

An excess relative rate (ERR) regression model was fitted of the form $\lambda(c, s, b, a, d)=\lambda_0(c, s, b, a)[1 + \beta d]$, where λ is the rate of death depending on country (c), sex (s), year of birth (b), attained age (a), and cumulative red bone marrow dose (d) in Gy in a linear dependence, λ_0 is the baseline mortality rate modelled through stratification, and β quantifies the ERR per Gy. Stratification on attained age and year of birth provides control for calendar year of death (noting that a decedent's year of birth and attained age identify the calendar year of death). Parameter estimates were obtained by Poisson regression methods. Cumulative doses were lagged to allow for an induction and latency period between exposure and death, by 2 years for the analysis of non-CLL leukaemia and separate types, and by 10 years for the analysis of lymphoma and multiple myeloma. These lag values were chosen a priori to facilitate comparison of results with those from previous analyses of haematological cancers in INWORKS.[6,15] Sensitivity analyses investigated the effect of different lag periods (2, 5, 10, and 15 years) and results were compared based on goodness of model fits.[16]

Further investigations were performed for non-CLL leukaemia mortality. The dose-response association was examined by fitting a regression model with indicator variables for cumulative dose categories, and ERRs were plotted against mean dose values. Departure of the dose-response relationship from linearity was formally tested by fitting alternative dose-response models: a linear-quadratic model ($ERR(d)=\beta_1 d+\beta_2 d^2$) and a quadratic model ($ERR(d)=\beta d^2$). We examined the dose-response association over restricted dose ranges by truncating the follow-up of workers when they had accumulated the maximum dose chosen (<300, <200, <100, and <50 mGy). Variations in the effect of cumulative dose on non-CLL leukaemia mortality across attained age categories (<60, 60–79, and ≥80 years), neutron monitoring status, and internal contamination monitoring flag were also assessed. We compared the effect of radiation dose on non-CLL leukaemia mortality among workers hired before 1958 with that among workers hired from

See Online for appendix 2

	France	UK	USA	INWORKS
Calendar years of follow-up	1968–2014	1955–2012	1944–2016	1944–2016
Workers	60 697	147 872	101 363	309 932
Sex				
Male	52 895	134 768	81 824	269 487
Female	7802	13 104	19 539	40 445
Follow-up (million person-years)	2·08	4·67	3·98	10·72
Males	1·80	4·27	3·17	9·24
Females	0·28	0·40	0·81	1·48
Deaths (all causes)	12 270	39 933	51 350	103 553
Leukemia excluding CLL	122	264	385	771
Chronic myeloid leukaemia	21	46	55	122
Acute myeloid leukaemia	54	160	221	435
Myelodysplastic syndrome	19	34	110	163
Acute lymphoblastic leukaemia	12	17	20	49
CLL	37	90	115	242
Non-Hodgkin lymphoma	160	387	599	1146
Hodgkin lymphoma	21	41	60	122
Multiple myeloma	74	186	267	527
Average duration of follow-up, years	34·2	31·6	39·3	34·6
Average age at end of follow-up, years	64·8	62·5	71·4	65·9
Average cumulative dose, mGy*	11·88	18·47	15·39	16·17
Males	13·29	19·84	18·33	18·09
Females	2·33	4·37	3·06	3·34
Exposed workers†	43 785 (72%)	131 253 (89%)	84 956 (84%)	259 994 (84%)
Males	40 272 (76%)	119 420 (89%)	71 600 (88%)	231 292 (86%)
Females	3513 (45%)	11 833 (90%)	13 356 (68%)	28 702 (71%)
Average cumulative dose (mGy)*‡				
All	16·47	18·47	18·36	19·28
Males	17·45	22·39	20·95	21·08
Females	5·17	4·84	4·48	4·71

Ethnic and racial backgrounds of the workers are not available in the cohort. CLL=chronic lymphocytic leukaemia. INWORKS=International Nuclear Workers Study. *To red bone marrow. †Those with at least one positive recorded dose. ‡Among exposed workers only.

Table 1: **Characteristics of the cohorts included in INWORKS: nuclear workers in France, the UK, and the USA, 1944–2016**

1958 onwards, as previous studies have raised concerns regarding workers hired in the early years of the industry;[17] and, we repeated this analysis using 1965 as the cutoff year. The a priori choice of a set of variables (ie, country, birth cohort, attained age, and sex) for modelling the baseline rate of death from non-CLL leukaemia was assessed by fitting models using alternative stratification strategies, considering socioeconomic status, duration of employment, year of hire, neutron monitoring status, and internal contamination status. We assessed the effect of each country by removing one at a time from the analysis. We estimated the excess number of deaths associated with radiation exposure, which we calculated as the difference between the fitted number of deaths within a stratum defined by levels of the stratification variables and the background number of deaths (obtained by multiplying the stratum-specific baseline mortality rate by the person-time in that stratum).

Consistent with prior analyses,[6,11,18] we report maximum likelihood estimates of ERR per Gy and associated 90% likelihood-based CI. When the likelihood-based CI could not be estimated, we report a Wald-type CI. We report the change in deviance upon inclusion of a term in the regression model as a likelihood ratio test statistic along with its associated p value, which provides a continuous measure of the fit of the model to the data.[19] All models were fitted with EPICURE software (version 1.81; Risk Sciences International, Ottawa, ON, Canada). Data protection regulations in Europe did not allow the transfer of raw personnel data between countries, and only aggregated data tables could be shared. Accordingly, descriptive statistics as medians and IQR were not calculable (table 1).

Role of the funding source

The funders of the study had no role in the study design, the data analysis and interpretation, the writing of the report, or in the decision to submit the paper for publication.

Results

Table 1 shows characteristics of the cohort. The study included 309 932 workers, of whom 269 487 (87%) were males and 40 445 (13%) females. On average, the workers were followed up for 35 years and were 66 years of age at the end of follow-up. The extension of follow-up resulted in a 30% increase in the number of person-years, which reached 10·72 million (8·22 million in the previous study).[5] The average cumulative red bone marrow dose was 16·2 mGy in the total cohort, and 19·3 mGy among 259 994 exposed workers (ie, those with at least one positive recorded dose, who represent 84% of the study cohort). At the end of the follow-up (Dec 31, 2016), 200 168 (65%) of workers were alive and 6211 (2%) had emigrated or were otherwise lost to follow-up for vital status ascertainment; 103 553 deaths were recorded, among them 771 were due to non-CLL leukaemia, 1146 to non-Hodgkin lymphoma, 122 to Hodgkin lymphoma, and 527 to multiple myeloma. Less than 2% (1772) of decedents had a missing or unknown underlying cause of death. Most deaths from leukaemia, lymphoma, and multiple myeloma were observed among workers who accumulated less than 5 mGy of dose, consistent with the distribution of person-years with respect to cumulative dose (appendix 2 p 3).

Using a linear ERR model, a positive dose-response association was obtained for non-CLL leukaemia (ERR per Gy 2·68, 90% CI 1·13 to 4·55), driven by a large radiation-related excess of chronic myeloid leukaemia (9·57, 4·00 to 17·9; table 2). A positive dose-response association was observed for myelodysplastic syndromes (3·19, 0·35 to 7·33) and for acute myeloid leukaemia and myelodysplastic syndromes combined (1·55, 0·05 to 3·42). The estimated ERR per Gy for multiple myeloma was 1·62 (90% CI 0·06 to 3·64, n=527). Estimates of association were quite imprecise

and not significant for acute myeloid leukaemia (0·75, –0·96 to 2·92, n=435), acute lymphoblastic leukaemia (4·25, –4·19 to 19·32, n=49), CLL (0·20, –1·81 to 2·21, n=242), Hodgkin lymphoma (0·60, –3·64 to 4·83, n=122) and non-Hodgkin lymphoma (0·27, –0·61 to 1·39, n=1146; table 2). Based on a simple linear ERR model, an estimated 40·4 deaths due to non-CLL leukaemia were in excess among the 771 observed (appendix 2 p 4). As males represent 87% of the cohort, the association between radiation dose and non-CLL leukaemia mortality was quantified in males only (ERR per Gy 2·55; 90% CI 1·02 to 4·41; n=691). In females, 74 (93%) out of 80 deaths from non-CLL leukaemia were observed in those who cumulated less than 20 mGy and the estimated ERR per Gy (16·13, 90% CI <0 to 49·65) was extremely imprecise.

Estimates of ERR per Gy of cumulative red bone marrow dose for death due to leukaemia, lymphoma, and multiple myeloma under different exposure lag assumptions are shown in appendix 2 (p 5). For non-CLL leukaemia the best model fit was obtained under a 5-year lag (ERR per Gy 2·95, 90% CI 1·32–4·91); under our a priori 2-year lag, model fit was poorer. For chronic myeloid leukaemia the best model fit was observed under a 5-year lag. For acute myeloid leukaemia, the best fit was obtained under a 15-year lag, although the estimate of association was imprecise. For acute lymphoblastic leukaemia, the shorter the lag, the better the model goodness of fit, while for CLL, non-Hodgkin lymphoma, and Hodgkin lymphoma, the longer the lag, the better the model fit (albeit with highly imprecise estimates of association for these outcomes). For multiple myeloma, the model fit was marginally better under a 5-year lag than under the a priori 10-year lag (while estimates of ERR per unit dose were similar under these lags).

The graphical representation of relative rates of death from non-CLL leukaemia by dose category did not show any strong deviation from linearity (figure), a conclusion supported by a formal comparison of the fit of the linear model to linear-quadratic and purely quadratic models. Model fit was not improved under a linear-quadratic model when compared with a linear model, and a quadratic model did not fit better than the linear ERR model. Similar conclusions were drawn for multiple myeloma: neither a linear-quadratic nor a pure quadratic model fitted the data better than a linear dose-risk model (appendix 2 p 10).

We investigated the radiation-associated risk of non-CLL leukaemia on restricted dose ranges; over the dose range 0–300 mGy, we observed a positive association, somewhat larger in magnitude than that obtained over the full dose range (ERR per Gy 3·10, 90% CI 1·22 to 5·35; appendix 2 p 6). The slopes of the dose-response relation over the 0–200 mGy and 0–100 mGy dose range were comparable in magnitude to (but less precise than) that estimated in the whole cohort; however, the estimated ERR per Gy diminished to 0·35 (90% CI –5·45 to 7·24) when the dose range was restricted to 0–50 mGy (appendix 2 p 6).

	Deaths	Lag assumption (years)	ERR per Gy*	90% CI
Leukemia excluding CLL	771	2	2·68	1·13 to 4·55
Chronic myeloid leukaemia	122	2	9·57	4·00 to 17·91
Acute myeloid leukaemia	435	2	0·75	–0·96 to 2·92
Myelodysplastic syndromes	163	2	3·19	0·35 to 7·33
Acute myeloid leukaemia with myelodysplastic syndromes	598	2	1·55	0·05 to 3·42
Acute lymphoblastic leukaemia	49	2	4·25	–4·19 to 19·32
CLL	242	2	0·20	–1·81 to 2·21†
Non-Hodgkin lymphoma	1146	10	0·27	–0·61 to 1·39
Hodgkin lymphoma	122	10	0·60	–3·64 to 4·83†
Multiple myeloma	527	10	1·62	0·06 to 3·64

CLL=chronic lymphocytic leukaemia. ERR=excess relative rate. INWORKS=International Nuclear Workers Study. *Linear ERR model stratified by country, birth cohort, age, and sex. †Wald-type CI (likelihood-based CI lower bound could not be estimated).

Table 2: **Estimates of ERR per Gy of cumulative red bone marrow dose, for death from leukaemia, myelodysplastic syndromes, lymphoma, and multiple myeloma in INWORKS**

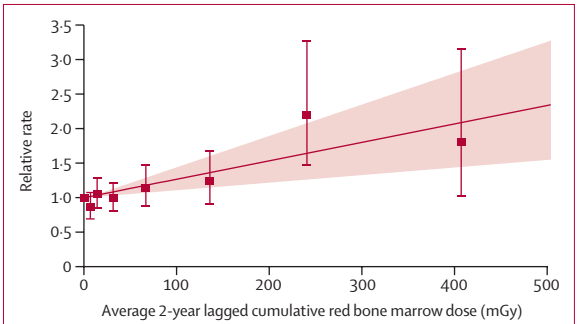

Figure: **Relative rates of mortality due to leukaemia (excluding chronic lymphocytic leukaemia) by category of 2-year lagged cumulative red bone marrow dose**

The vertical bars indicate 90% CIs, and the solid line is the fitted linear excess relative rate of leukaemia with dose (dotted lines depict 90% CI). The model is stratified on country, sex, birth cohort, and attained age.

Attained age showed a modifying effect on the dose-response association for non-CLL leukaemia, although not significantly, with an increasing ERR per Gy with increasing attained age (appendix 2 p 7). Consistent with this result, when excluding years of follow-up from age 80 years onwards, the slope of the dose-response relationship decreased (ERR per Gy 1·71, 90% CI 0·09 to 3·72; n=614; not shown).

We examined the impact of neutron monitoring status and internal contamination status on the dose-response association for non-CLL leukaemia but observed no significant modifying effect for either neutron monitoring status or for internal contamination status (appendix 2 p 7).

We compared the ERR of death from non-CLL leukaemia as a function of the date of hire and we observed no differences between the dose-response

	Deaths	ERR per Gy*	90% CI
Previous INWORKS report (308 297 workers to 8·2 million person-years)[6]			
Leukemia excluding chronic lymphocytic leukaemia†	531	2·96	1·17 to 5·21
Non-Hodgkin lymphoma‡	710	0·47	−0·76 to 2·03
Hodgkin lymphoma‡	104	2·94	NE to 11·49
Multiple myeloma‡	293	0·84	−0·96 to 3·33
Current INWORKS report (309 932 workers to 10·7 million person-years)			
Leukemia excluding chronic lymphocytic leukaemia†	771	2·68	1·13 to 4·55
Non-Hodgkin lymphoma‡	1146	0·27	−0·61 to 1·39
Hodgkin lymphoma‡	122	0·60	NE to 6·67
Multiple myeloma‡	527	1·62	0·06 to 3·64

ERR=excess relative rate. NE=not estimated. INWORKS=International Nuclear Workers Study. *Stratified by country, birth cohort, age, and sex. †2-year lagged cumulative dose. ‡10-year lagged cumulative dose.

Table 3: **Comparison of estimates of ERR per Gy of red bone marrow cumulative dose for death due to leukaemia, lymphoma, and multiple myeloma in different updates of INWORKS**

associations by hire date, whether for a cutoff date of 1958 or a cutoff date of 1965 (appendix 2 p 7).

The effect that a single country could have on the non-CLL leukaemia results was investigated by excluding one country at a time from the analysis: excluding France or the USA decreased the estimated ERR per unit dose (ERR per Gy 2·17, 90% CI 0·68–3·99 without France and 2·04, 0·11–4·59 without the USA) and excluding the UK had an opposite effect (4·33, 1·94–7·32; appendix 2 p 9). We found some heterogeneity among the national risk estimates that was no longer observed when attained age was restricted to younger than 80 years (results not shown).

Upon further adjustment for socioeconomic status, duration of employment, or year of hire, the estimated ERR per unit dose changed by less than 10%; upon further adjustment for neutron monitoring status the estimated ERR per Gy diminished to 2·30 (90% CI 0·64–4·43), whereas upon adjustment for internal contamination status the estimated ERR per Gy increased to 3·28 (1·50–5·48; appendix 2 p 8).

Table 3 shows the comparison between this updated analysis and the previous INWORKS estimates;[6] the extended follow-up resulted in a 45% (771 *vs* 531 in the previous analysis) increase in non-CLL leukaemia deaths, 61% (1146 *vs* 710) increase in non-Hodgkin lymphoma deaths and 17% (122 *vs* 104) increase in Hodgkin lymphoma deaths, and an 80% (527 *vs* 293) increase in multiple myeloma deaths.

Discussion

In INWORKS, we report an association between low-dose ionising radiation and non-CLL leukaemia mortality, driven by a large ERR of chronic myeloid leukaemia per unit red bone marrow dose. The association between non-CLL leukaemia mortality and cumulative dose is reasonably described by a linear dose-response model. For the first time, we examined mortality due to myelodysplastic syndromes in this cohort, and a positive association was observed with cumulative dose. There also is evidence of a positive association between radiation dose and multiple myeloma mortality (albeit with wide CIs), whereas there is minimal evidence of association between radiation dose and death from non-Hodgkin lymphoma or Hodgkin lymphoma. A strength of this update of INWORKS when compared with the previous analysis,[6] is that the precision of ERR estimates has improved, with narrower CIs for most outcomes examined (table 3); for non-CLL leukaemia, the magnitude of the estimate is consistent with the value reported in the previous analysis, for lymphoma the current estimates are lower than in the previous analysis, and for multiple myeloma, the magnitude of the estimate of association is twice as large as that reported in our previous INWORKS analysis.

The Radiation Effects Research Foundation Life Span Study (known as the Life Span Study, LSS) of Japanese atomic bomb survivors serves as an important basis for the international radiation protection system.[20] Although the acute high dose rate radiation exposures caused by the bombs differ from the protracted low-dose rate exposures typically received by nuclear workers, our estimate of the ERR per Gy absorbed dose to the red bone marrow for death from leukaemia was of similar magnitude to the estimate of ERR per Gy reported in the 2021 analyses of the LSS: when restrictions were made on the study population to make it comparable with the INWORKS population features, the ERR per Gy in the LSS was 2·75 (90% CI 1·73–4·21)[21] based on a linear model, which is very close to the estimated ERR per Gy in the present INWORKS analysis (ERR per Gy 2·68, 90% CI 1·13–4·55). There are differences however, in that a linear-quadratic model with an upward curvature described the data better in the LSS, whereas no departure from linearity is observed in INWORKS (albeit over a much narrower dose range than that examined in the LSS), and in the LSS the ERR per Gy decreased with attained age, whereas the opposite is true in INWORKS (noting that INWORKS considers only exposures at adult working ages [≥20 years] whereas the LSS involves people exposed at all ages).

Other epidemiological studies have investigated radiation induced risk of leukaemia.[1,3] Some reported positive dose-response associations for non-CLL leukaemia,[3,22,23] although others encompassed small numbers of cases or were based on narrow dose distributions and yielded imprecise risk estimates.[3,22,24]

The UK NRRW study examined non-CLL leukaemia incidence and reported a significant dose-response relationship (ERR per sievert [Sv] 1·38, 90% CI 0·04–3·34) in male workers (who represent more than 90% of the cohort), with a strong association for chronic myeloid leukaemia (6·77, 2·13–15·4).[18] The risk coefficients per unit dose are lower than those estimated in INWORKS, but in the NRRW the authors used dose equivalents in Sv and not absorbed red bone marrow dose.

We report a positive association between radiation and myelodysplastic syndromes mortality. Myelodysplastic syndromes is now considered to be a disease of neoplastic nature and the boundary between myelodysplastic syndromes and acute myeloid leukaemia has become thinner.[25] Until the mid-1980s, cases were often misdiagnosed as acute myeloid leukaemia. A positive finding was observed between external radiation and myelodysplastic syndromes in the Nagasaki atomic bomb survivors, with an ERR per Gy of 4·3 (95% CI 1·6–9·5),[26] which is compatible with association observed in INWORKS.

We observed minimal evidence of association between radiation dose and non-Hodgkin lymphoma mortality (ERR per Gy 0·27, 90% CI –0·61 to 1·39). Few epidemiological studies have reported a significant positive dose-risk association for non-Hodgkin lymphoma, whether for medical, environmental, or occupational exposures.[1] In 2013 report from the LSS, Hsu and colleagues[2] showed a non-significantly increased risk of non-Hodgkin lymphoma incidence in men (ERR per Gy 0·46, 95% CI –0·08 to 1·29; p=0·11), but not in women. The UK NRRW cohort reported a significant association between radiation dose and non-Hodgkin lymphoma incidence (ERR per Sv 1·11, 95% CI 0·02 to 2·60; p=0·045; n=711),[10] but not mortality (ERR per Sv 1·31, 90% CI –0·25 to 3·77; n=353).[9] A positive association also was reported in analyses of mortality among US nuclear workers for all lymphoma combined (ERR per Sv 1·8, 95% CI 0·03 to –4·4).[27]

A recent study[28] assessed associations between radiation and incidence of lymphoid neoplasms by histological subtype[29] in the LSS cohort. A significant association was reported for all non-Hodgkin lymphoid neoplasms (ERR per Gy 0·54, 95% CI 0·14–1·09) although a direct comparison with our results is complicated because of differences in outcome classifications. Evidence of a positive association between ionising radiation dose and lymphoid malignancies also has been reported in a study of patients exposed to CT scan during childhood.[30]

We observed minimal evidence of association between red bone marrow dose and Hodgkin lymphoma mortality, consistent with the conclusions of the United Nations Scientific Committee on the Effects of Atomic Radiation[1] and studies of accidental[2] and occupational[31] exposures. In the LSS, a non-significant association with Hodgkin lymphoma incidence was reported of similar magnitude to that reported in INWORKS (ERR per Gy 0·61; 95% CI less than –0·09 to 7·17; n=15).[28]

With updated follow-up the number of deaths due to multiple myeloma increased by 80%. An interesting new result in this study is evidence of a positive association between radiation dose and multiple myeloma mortality (albeit with wide CIs); notably, however, the association is negligible upon excluding the USA from the pooled analysis (appendix 2 p 9). Our estimated ERR per Gy is larger than, but statistically compatible with, the estimate of the radiation dose-multiple myeloma mortality association reported in the LSS (ERR per Gy 0·54, 95% CI –0·04 to 1·58),[32] and smaller than, but statistically compatible with, the estimate of the radiation dose-multiple myeloma incidence association in the UK NRRW (ERR per Gy 2·63, 95% CI 0·30 to 6·37).[10]

The study's strengths lie in its large size, long duration of follow-up, and individual dose estimates based on personal dosimetry.[13] Uncertainties in dose estimates are certainly larger in earlier periods of employment, when dosimeters were less accurate than contemporary ones.[13] We investigated whether excluding workers with earlier date of first employment affected the estimate of the slope of the dose-response relationship for non-CLL leukaemia but found minimal evidence that associations were sensitive to such exclusions.

Despite its large size, the cohort is limited to inform on risks in females, because whatever the outcome, the few deaths were predominantly (83–100% depending on the outcome) observed in women who had accumulated less than 20 mGy (result not shown).

We have no precise data on doses due to incorporation of radionuclides such as uranium or plutonium, but considering workers' status with regard to a possible contamination did not change the dose-response relationship between external dose and non-CLL leukaemia mortality (appendix 2 p 8). We also found that considering neutron monitoring status did not change the dose-response relationship.

Information on other potential confounders is limited in INWORKS. Considering agents with sufficient evidence of carcinogenicity,[33] excluding alkylating agents and x-rays and gamma (γ) rays, there are three agents with sufficient evidence of carcinogenicity for non-lymphocytic leukaemia in human: benzene, formaldehyde, and tobacco smoking.[33] While formaldehyde is not widely used in the nuclear industry (except perhaps in nuclear waste processing), benzene cannot be ruled out as a potential confounder. Previous studies in US nuclear workers found that early workers (ie, workers first hired in the first decades of nuclear industry) were at greater risk of benzene exposure and when these workers were excluded, there was no potential for substantial confounding.[34] We showed that excluding early workers did not significantly impact the association between radiation and non-CLL leukaemia mortality, which argues against the hypothesis of strong confounding by benzene. In a sensitivity analysis, we adjusted for duration of employment, which led to minimal change in the estimate of association between radiation dose and mortality due to non-CLL leukaemia (appendix 2 p 8), arguing against substantial confounding due to preferential retention of workers in better health (sometimes termed healthy worker survivor bias) for this outcome. As for tobacco smoking, a 2023 analysis of INWORKS[7] reported that radiation dose had

minimal association with chronic obstructive pulmonary disease, an outcome strongly associated with smoking; this provides indirect evidence against the hypothesis of strong confounding by smoking.

In contrast to a previous analysis of non-CLL leukaemia mortality in this population,[6] we observed evidence of heterogeneity in association by country (appendix 2 p 9). The estimate for the French cohort appeared higher than for the UK and US cohorts; in the French cohort the effect of attained age is particularly significant.[11] When the age at the end of follow-up was constrained to younger than 80 years, heterogeneity by country reduced markedly. Outcome misclassification among older adults could contribute to heterogeneity in association by country (and its reduction upon excluding those at the oldest attained ages).

In conclusion, studies of people exposed to low doses of radiation add to our understanding of radiation risks at the exposure levels of contemporary concern, and thus can inform radiation protection efforts.[35] The United Nations Scientific Committee on the Effects of Atomic Radiation[3] and the US National Cancer Institute[22] have examined studies on leukaemia risk after low-dose external exposure and concluded that most of them were consistent with a positive dose–risk relationship. This analysis of INWORKS supports those findings. Nevertheless, the absolute excess risk remains low at low doses: in a population of 10 000 workers exposed to an average occupational dose of 16 mGy, we would expect 1·3 non-CLL deaths attributable to exposure (among 25 non-CLL leukaemia deaths) over a 35-year period. The evidence of associations between cumulative radiation dose and multiple myeloma and myelodysplastic syndromes in INWORKS should be further examined in future studies.

Contributors

DBR conceived the study. DBR, KL, DL, MG, RH, KK-R, SB, RDD, IT-C, AK, and MKSB developed the research questions and designed the study. KL and DL worked on provision of the French data; KK-R, SB, RDD, and MKSB worked on provision of the US data; MG and RH worked on provision of the UK data. MM was responsible for data management and processing as well as some analyses. IT-C was responsible for the dosimetry. KL did the statistical analysis and produced the initial draft of the manuscript, which was revised and approved by all authors. KL and MM had access to the raw data for France, RDD, KK-R, SB, and MM had access to the raw data for the US, and MG and RH had access to the raw data for the UK. Tabulated data were accessible to all co-authors. KL and DBR had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

For reasons of ethics and permissions from different agencies, the data are maintained at the International Agency for Research on Cancer (Lyon, France) and cannot be made available outside of the agency. Data use requests may be directed to the appropriate national authorities. The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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