Risk of Leukemia Associated with Protracted Low-Dose Radiation Exposure: Updated Results from the National Registry for Radiation Workers Study

Authors: Gillies, Michael, Haylock, Richard, Hunter, Nezhat, and Zhang, Wei

Source: Radiation Research, 192(5) : 527-537

Published By: Radiation Research Society

URL: https://doi.org/10.1667/RR15358.1

RADIATION RESEARCH **192**, 527–537 (2019)
0033-7587/19 $15.00

DOI: 10.1667/RR15358.1

Risk of Leukemia Associated with Protracted Low-Dose Radiation Exposure: Updated Results from the National Registry for Radiation Workers Study

Michael Gillies,[1] Richard Haylock, Nezhat Hunter and Wei Zhang

Public Health England Centre for Radiation, Chemical and Environmental Hazards (PHE-CRCE), Chilton, United Kingdom

Gillies, M., Haylock, R., Hunter, N. and Zhang, W. Risk of Leukemia Associated with Protracted Low-Dose Radiation Exposure: Updated Results from the National Registry for Radiation Workers Study. *Radiat. Res.* 192, 527–537 (2019).

While the link between risk of leukemia and acute radiation exposure is well established for large doses received acutely, uncertainty remains around the translation of these risk estimates to occupational exposure scenarios where the doses are low and accumulated over time, possibly over many years. We present leukemia incidence and mortality radiation risk estimates derived from the National Registry for Radiation Workers, which is a large cohort of occupationally exposed workers from the United Kingdom (UK). The cohort comprised 173,081 workers from the UK who were monitored for occupational exposure to radiation. The cohort was followed for a total of 5.3 million person-years and the incidence and mortality due to leukemia was identified through to the end of follow-up in 2011. Poisson regression was used to investigate the relationship between cumulative radiation dose and leukemia mortality and incidence rates using excess relative risk (ERR) and excess additive risk (EAR) models. The results of this work showed a collective dose of 4,414 person-Sv accumulated by the cohort with an average cumulative dose of 25.5 mSv. Among male workers both the ERR and EAR models showed evidence of increased leukemia risk (excluding chronic lymphatic leukemia) associated with increasing cumulative dose. The ERR was 1.38 per Sv (90% CI: 0.04; 3.24) and EAR was 1.33 per 10,000 person-year-Sv (90% CI: 0.04; 2.89) when a linear model was used. These excess risks were driven by increased risks for chronic myeloid leukemia [ERR/Sv = 6.77 (90% CI: 2.14; 15.44)]. In conclusion, this study provides further evidence that leukemia risks may be increased by low-dose and protracted external radiation exposure. The risks are generally consistent with those observed in the atomic bomb survivor studies, as well as with risk coefficients on which international radiation safety standards, including the dose limits and constraints used to control exposures, are based.

INTRODUCTION

In the first few years after the atomic bombings of Hiroshima and Nagasaki an excessive number of survivors developed leukemia (*1*); this excess persisted in long-term follow-up studies of the survivors (*2–4*). While these studies helped to establish a link between leukemia and acute radiation exposures, there remains uncertainty over the translation of these risks to different populations and to the protracted low-dose and dose-rate exposures typically received by workers in the nuclear industry. Despite this, risk coefficients derived from studies of the atomic bomb survivors still largely form the basis for international radiation safety standards, including the dose limits and constraints used to control exposures (*5–10*) to workers and the public.

Nuclear worker studies around the world (*11–13*) have been undertaken to assess directly the risks of low-dose and low-dose-rate radiation exposure for determining the validity of risk extrapolations from the acute exposure studies used to define protection standards. The National Registry for Radiation Workers (NRRW) was started in 1976 to provide direct evidence of the risks to health from occupational exposure to chronic low-dose external radiation in the UK. The third analysis of the NRRW (NRRW-3) (*14, 15*) demonstrated a healthy worker effect (HWE), as seen previously (*16, 17*) in this and many other occupationally exposed cohorts. In that analysis, evidence was also found of increased risk of leukemia (excluding chronic lymphocytic leukemia) and solid cancers associated with external radiation exposure that were consistent with estimates from the Life Span Study (LSS) of the Japanese atomic bomb survivors. More recently, an updated analysis of cancer end points in the NRRW-3 cohort (*18*) continued to show risk values that were consistent with LSS estimates. Presented here is a similar updated analysis of leukemia

Editor's note. The online version of this article (DOI: https://doi.org/10.1667/RR15358.1.S1) contains supplementary information that is available to all authorized users.

[1] Address for correspondence: Department of Radiation Effects, Centre for Radiation Chemical and Environmental Hazards, Public Health England, Oxfordshire, OX11 0RQ, UK; email: michael.gillies@phe.gov.uk.

mortality and incidence end points in the NRRW-3 cohort with follow-up extended by ten years.

METHODS

The NRRW-3 cohort has been described in detail elsewhere (*15, 19*). For completeness, a summary is provided here. The cohort is comprised of individuals monitored for occupational exposure to external ionizing radiation, who were employed by participating organizations and for whom individual dose records were kept. Participating employers, which were also in the previous NRRW-3 analysis (*15*), are: the Atomic Weapons Establishment (AWE), British Nuclear Fuels Ltd. (BNFL), the United Kingdom Atomic Energy Authority (UKAEA), British Energy Generation and Magnox Electric sites in England and Wales and Scotland, the UK Ministry of Defence (MoD), GE Healthcare, Rolls-Royce submarines and a number of other smaller research organizations (*15*). Data collected from employers consisted of individual identifiers, date of birth, gender and industrial classification (industrial or non-industrial where available, a surrogate for socioeconomic status broadly equivalent to manual/non-manual occupations), internal exposure (monitored or not-monitored for intakes of radioactive materials, primarily uranium, plutonium and tritium), calendar periods of employment and exposure and external radiation dose histories.

This analysis focuses on doses from penetrating radiation at the surface of the body as measured from personal dosimeters. The vast majority of the doses are associated with X rays and gamma rays although a number of workers will have also received a component of beta particle and neutron exposure in their measured dose. As with the previously reported analysis, since doses were recorded mainly for regulatory purposes, a number of corrections have been applied to produce a more consistent set of dose estimates for epidemiological analysis (*19*). All dose estimates are recorded in sieverts (Sv) and are reported in either Sv or millisieverts (mSv).

The cohort included in this analysis is essentially the same as that reported previously (*14, 18, 20*) although there are a number of small differences mainly due to changes in follow-up information over time and the inclusion of 10 additional years of dosimetry information. The analysis cohort consists of 173,081 workers. A breakdown of the cohort by first employer and cumulative dose is given in Table 1.

Follow-up Data and Ascertainment of Causes of Death and Cancer Incidence

The cohort was followed to ascertain vital status through to the end of 2011. As was the case in prior analysis of this cohort, the end of follow-up was chosen to ensure that as complete as possible dosimetry information was available up to at least two years before the end of follow-up, since two years was shortest lag period used in the analysis of radiation exposure and leukemia risk. Start of follow-up for each worker was defined as the later of the following:

1. Start date of radiation work at a participating employer;
2. Date when monitoring first became available for an employer (e.g., 1961 for the MoD);
3. January 1, 1955;
4. January 1, 1971 (only used in supplementary analysis which used cancer information alone).

Follow-up prior to 1955 was excluded due to indications that follow-up information prior to that date may not be complete (*14, 15*). In the supplementary analysis based on cancer incidence information alone (i.e., where mortality information was ignored) the earliest date of follow-up was taken to be January 1, 1971, since cancer registration information is not routinely available from national tracing organizations prior to that date.

In the main dose-response analyses, the end of follow-up was defined as the earliest date of any of the following events:

1. Date of last contact (untraced and emigrated workers);
2. December 31, 2011;
3. Date of death (mortality);
4. Date of cancer first incidence (excluding non-melanoma skin cancers).

The only exceptions to this rule were in supplementary analyses based on mortality information alone where cancer incidence events were ignored when censoring follow-up.

The follow-up data, including vital status, causes of death and cancer incidence information for the cohort, were provided to Public Health England (PHE) by NHS Digital (formerly the Health and Social Care information Centre) and by National Records of Scotland.

Information on underlying cause of death and cancer incidence registrations was coded according to the appropriate revision of the International Classification of Diseases (ICD). Results are presented for all leukemias combined, all leukemias excluding chronic lymphatic leukemia (non-CLL) and for the four main subtypes of leukemia and three groupings of unspecified leukemias: acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), unspecified lymphoid leukemia, unspecified myeloid leukemia and unspecified leukemia. A full tabulation of the leukemia disease groupings considered in this study is given in Supplementary Table S1 (https://doi.org/10.1667/RR15358.1.S1) along with associated ICD codes that were used to create these groupings. The main dose-response analysis focuses on non-CLL, because the number of events in some of the leukemia subtypes is too small to obtain robust estimates and because of prior evidence that CLL is not related to radiation exposure.

Statistical Methods

The statistical analysis was split into two parts:

1. An exploratory external analysis looking at how overall leukemia mortality and incidence rates in the cohort compared with national figures.
2. The dose-response analysis which concentrated on how the risks varied with occupational radiation exposure.

In the external analysis, standardized mortality ratios (SMRs) and standardized incidence ratios (SIRs) were calculated to compare leukemia mortality and incidence rates in the cohort with those expected on the basis of mortality and incidence statistics for the population of England and Wales as a whole after adjustment for age, gender and calendar year (*21*). This external analysis includes all workers in the cohort, although in sub-analyses rates were separately examined for male and female workers.

Among females (9.8% of the cohort) there was an insufficient number of leukemia cases (non-CLL: 17 deaths, 22 incidences) and the doses were too small (mean dose of 5.6 mSv) to allow meaningful analysis. Therefore, the main dose-response analysis was based on male workers only.

To perform the analysis, the data were organized in multidimensional person-years tables with the number of person-years accumulated and the number of leukemia events recorded in each cell. For the main dose-response analysis the data in this tabulation were cross-classified by first employer [15 groups; see ref. (*15*) for further details], attained age (15–19, 20–24, … 89–84, 85+), calendar period (1955–1959, 1960–1964, …. 1995–1999, 2000–2001, 2002–2006, 2007–2011), gender, industrial status (industrial, non-industrial, unknown), internal radiation monitoring status (monitored for internal radiation, non-monitored), and two-year lagged cumulative dose (eight categories with cut-off points at 5, 10, 20, 50, 100, 200 and 400 mSv).

The goal of the statistical analysis was to assess how the rate of leukemia mortality and incidence changes in relationship to cumulative doses from occupational radiation external exposure, taking account of available information on potential confounding factors such as gender, attained age, birth cohort, calendar period,

TABLE 1
Summary for the NRRW Cohort by First Employer

Employer	No. of workers by cumulative dose (mSv) <10	10–59	50–100	100+	Total no. of workers	Mean dose	Collective dose (mSv)	Person-years (person-Sv)
UKAEA	14,858	7,989	2,379	2,313	27,539	34.3	944.8	972,854
BNFL	18,548	11,719	4,000	5,811	40,078	54.7	2,192.2	1,275,453
AWE	12,127	2,247	283	162	14,819	8.4	124.6	439,698
MOD	54,955	6,311	1,394	1,171	63,831	8.5	542.0	1,844,114
British Energy Generation (England and Wales)	6,204	5,378	1,163	613	13,358	24.4	325.7	445,228
British Energy Generation (Scotland)	1,845	794	320	185	3,144	23.4	73.5	75,062
GE Healthcare	2,648	709	223	307	3,887	32.5	126.3	97,704
Research organizations[a]	2,298	683	101	42	3,124	11.1	34.7	94,784
Rolls-Royce	2,432	640	166	63	3,301	15.1	49.9	85,915
Total	115,915	36,470	10,029	10,667	173,081	25.5	4,413.6	5,330,813

[a] This employer group consists of a number of research organizations; further details can be found elsewhere (*15*).

socioeconomic status, duration of employment, employer/facility of employment and exposure to other forms of radiation. Poisson regression models were used to estimate the excess relative risk (ERR) and excess absolute risk (EAR) for leukemia mortality and incidence associated with cumulative external radiation dose.

The age-specific risk, $\lambda_{(a,\ c,\ i,\ f,\ d)}$, where a is the attained age, c is calendar period, f is the first employer, i is the industrial status and d is the cumulative external dose, was defined as follows for the two models.

The form of the ERR models was:

$$\lambda\left(_{a,c,i,f,d}\right) = \lambda_0\left(_{a,c,i,f}\right)[1 + \mathrm{ERR}(_d)], \quad (1)$$

while that for the EAR models was:

$$\lambda\left(_{a,c,i,f,d}\right) = \lambda_0\left(_{a,c,i,f}\right) + \mathrm{EAR}(_d) \quad (2)$$

The ERR estimates are expressed per Sv while the EAR values estimate the excess leukemia cases per 10,000 person-year-Sv (Py-Sv). Fully parametric, semi-parametric and stratified models were all considered for the baseline hazard function (λ_0) for the ERR model and these produced broadly similar results. Most of ERR model results are presented using a model containing stratified adjustment for age, calendar year, first employer and industrial status. However, the EAR model used a parametrically-specified background including adjustments for the same factors of attained age, calendar time, industrial status and first employer.

For the main analyses, the relative rate was quantified as a linear function of cumulative dose, where $\mathrm{ERR}(d) = \beta d$. To allow for an induction and latency period between exposure and death/incidence and to enable comparison with previous study results, cumulative dose was lagged by two years in the main analysis. Although most of the ERR estimates presented here are based on a linear ERR model ($\mathrm{ERR}(d) = \beta d$), the linearity of the estimates was also tested by comparing the relative fit of the linear model to linear-quadratic ($\mathrm{ERR}(d) = \beta_1 d + \beta_2 d^2$), quadratic ($\mathrm{ERR}(d) = \beta d^2$) and linear exponential models ($\mathrm{ERR}(d) = \beta_1 d \exp(\beta_2 d)$).

In addition, analyses were performed to evaluate gender, internal radiation monitoring status and attained age as potential effect modifiers. Due to computational constraints on the ERR parameter and low power, the supplementary analyses, in which the modifying effects of gender were evaluated, were based on comparing the deviation of the multiplicative relative risk model with a single exponential dose parameter against a model that included an additional parameter that allowed for gender-specific risks.

The variation in risk over follow-up was examined by truncating analyses at 2011, 2006, 2001 and 1996, respectively, and looking at risks across time since first exposure. Temporal variation in the effect of exposure was examined through the analysis of age-at-exposure and time-since-exposure windows. Defined windows were used to evaluate variation in risk by age-at-exposure (<30, 30–49 and 50+ years) and time-since-exposure (2–24 and 25+ years). For age-at-exposure and time-since-exposure, the cumulative dose received in each of the categories was modeled jointly, with each window categorized into the same set of dose categories as used in the main lagged analysis, and the fit of this model was tested against that of the standard model with two-year lagged total cumulative dose. As with previous leukemia analyses in this cohort, the main analysis was based on two-year lagged doses, but results for alternative lagging periods of 10, 20, 25 and 30 years were also considered in supplementary analyses.

Parameter estimates were computed using maximum likelihood methods. Hypothesis tests and confidence intervals were based on likelihood ratio tests and direct evaluation of the profile likelihood. We have reported 90% confidence intervals (90% CI) for the ERR and EAR parameter estimates to be consistent with previous studies. The results may thus be interpreted as a one-sided test at the 5% level of statistical significance. All analyses were performed using the AMFIT module of the EPICURE software (*22*). Due to computational constraints (i.e. the small number of events) most of the analysis focused on the overall grouping of non-CLL and EAR results are only presented for this disease grouping.

RESULTS

The study population for this analysis consisted of 173,081 workers (Table 1) who accrued 5.3 million person-years of follow-up and a collective dose of 4,414 person-Sv. While the average cumulative dose was 25.5 mSv, distribution of dose was very skewed; most workers were exposed to relatively low levels of radiation, with 115,915 (67%) workers receiving less than 10 mSv of cumulative dose. However, the cohort also included workers with moderate to high cumulative occupational exposures; 10,667 (6.2%) workers accrued doses of more than 100 mSv, 1,529 (0.9%) more than 400 mSv and 70 workers above 1 Sv from exposures over their working lifetime.

External Analysis

A total of 375 people were known to have died with leukemia as the underlying cause of death by the end of

TABLE 2
Standardized Mortality and Incidence Ratios (SMR/SIRs) by Leukemia Subtype

	Mortality[a]				Incidence[b]			
	Number of deaths				Number of incidences			
Leukemia subtype	Observed	Expected[c]	SMR	95% CI	Observed	Expected[d]	SIR	95% CI
ALL	21	26.9	78.2	48.4; 119.5	28	28.2	99.5	66.1; 143.8
CLL	89	96.1	92.6	74.4; 113.9	251	237.6	105.6	93.0; 119.5
Unspecified lymphatic	7	8.1	86.8	34.9; 178.9	41	33.0	124.1	89.1; 168.4
AML	164	199.0	82.4	70.3; 96.1	186	208.6	89.2	76.8; 102.9
CML	56	59.8	93.7	70.8; 121.7	86	85.0	101.2	80.9; 125.0
Unspecified myeloid	5	5.2	95.9	31.1; 223.9	17	10.4	163.8	95.4; 262.2
Unspecified leukemia	33	25.3	130.6	89.9; 183.4	23	26.6	86.4	54.8; 129.7
All leukemia	375	420.2	89.2	80.4; 98.7	636	629.4	101.0	93.3; 109.2
Non-CLL	286	324.1	88.2	78.3; 99.1	385	391.8	98.3	88.7; 108.6

[a] Mortality covers the period 1955–2011.
[b] Incidence analysis based on the period 1971–2011.
[c] The expected number of deaths is based on England and Wales figures.
[d] The expected number of leukemia incidences are based on England and Wales for 1971–2006 and England-only figures for 2007–2011.

follow-up, and of these, 286 (76%), were attributed to non-CLL types (Table 2). Despite incidence data only being routinely available from 1971 there were considerably more leukemia incidences registered (636) than mortality events and 61% (385) of these incidences were attributed to non-CLL types.

For mortality, none of the leukemia subtypes showed evidence of increased risks compared to national rates (Table 2) and indeed the rates for non-CLL and AML were somewhat below the national level [non-CLL: SMR = 88 (95% CI: 78; 99); AML: SMR = 82 (95% CI: 70; 96)]. However, unlike mortality, there was no evidence that the non-CLL incidence rate was below national levels [SIR = 98 (95% CI: 89; 109)]. Among the leukemia subtypes a similar pattern was observed with no evidence of increased incidence compared to national rates. Leukemia SMRs and SIRs for male workers were very similar to the overall figures (Supplementary Table S2; https://doi.org/10.1667/RR15358.1.S1), while the small number of leukemias among female workers (Supplementary Table S3) provided no evidence of increased risks for any of the leukemia subtypes.

Dose Response Analysis

Leukemia subtype-specific ERR/Sv estimates are presented with respect to cumulative external dose lagged two years in Table 3. For non-CLL, a statistically significant ERR [ERR = 1.38 (90% CI: 0.04; 3.34)], was found. This excess risk was largely driven by CML [ERR = 6.77 (90% CI: 2.14; 15.44), 88 cases]. Among other leukemia subtypes there was little evidence of increased risks, and as expected, CLL [ERR = –0.60 (90% CI: <0; 0.65)] showed no evidence of increased risk in relationship to external dose.

The shape of the dose response for non-CLL was examined by comparing the dose category-specific ERR estimates to the ERR/Sv estimate from the linear model (Fig. 1), which indicates that a linear model adequately approximated the dose-response function, although much of the evidence of increased risk came from doses in excess of 100 mSv. This was confirmed by fitting alternative, linear-quadratic and linear exponential models, none of which markedly improve model fit ($P > 0.50$). The linear model was also found to have a lower deviation than the pure quadratic model. To assess the trend over the lower cumulative dose range, we estimated the linear ERR over restricted cumulative dose ranges of 0–400 mSv [ERR = 1.86 (90% CI: –0.13; 4.54)], 0–200 mSv [ERR = 2.51 (90% CI: –0.44; 6.39)] and 0–100 mSv [ERR = 0.53 (90% CI: –3.78; 6.21)]. These estimates are all consistent with the unrestricted estimate, although as anticipated, the uncertainty on estimates increases with decreasing dose range.

As mentioned previously, the main dose-response analysis was based only on male workers since there was insufficient information among females to produce meaningful results using the linear ERR model. Given this lack of information, it

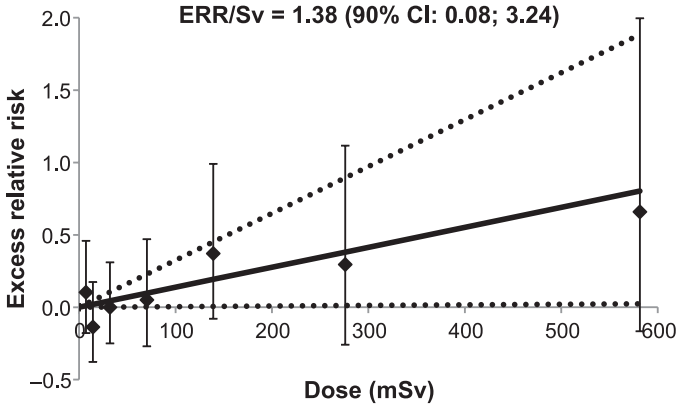

FIG. 1. Non-CLL ERR estimates and 90% CI by two-year-lagged external cumulative dose category with linear ERR/Sv estimate and associatec 90% CI reference lines.

TABLE 3
Male Leukemia Incidence in Relationship to External Radiation Dose: ERR/Sv Estimates, Observed and Expected Number of Leukemia Cases from Poisson Regression Analysis

Leukemia subtype	Observed cases [expected cases[a]] by cumulative external dose (mSv), two-year lag							Total	ERR/Sv[b] (90% CI)	*P* value[c]
	<10	10–20	20–50	50–100	100–200	200–400	>400			
ALL										
Observed	14	2	4	3	1	1	0	25	1.79 (<–7.19; 25.80)	0.377
Expected	[15.5]	[2.4]	[2.8]	[1.5]	[1.0]	[0.5]	[0.2]	[23.8]		
CLL										
Observed	119	32	37	24	13	8	3	236	–0.60 (<–1.69; 0.65)	0.819
Expected	[121.8]	[29.8]	[39.6]	[22.5]	[15.1]	[9.0]	[5.1]	[242.8]		
Other lymphatic										
Observed	21	5	7	2	1	0	0	36	–0.60 (<–6.38; 1.56)	0.818
Expected	[22.7]	[3.7]	[4.7]	[2.6]	[1.7]	[0.9]	[0.6]	[36.8]		
AML										
Observed	109	12	25	11	13	6	1	177	–0.19 (<–1.84; 2.28)	0.569
Expected	[105.2]	[18.4]	[24.2]	[14.0]	[9.2]	[4.7]	[2.4]	[178.2]		
CML										
Observed	49	9	9	6	6	3	6	88	6.77 (2.13; 15.44)	<.001
Expected	[46.5]	[7.5]	[9.0]	[4.9]	[2.7]	[1.6]	[0.9]	[73.1]		
Other myeloid										
Observed	11	3	1	1	0	1	0	17	–0.55 (<–9.04; 7.44)	0.630
Expected	[8.9]	[2.3]	[3.0]	[1.7]	[0.8]	[0.5]	[0.2]	[17.3]		
Unspecified leukemia										
Observed	21	3	2	5	2	1	0	34	0.74 (<–5.33; 13.93)	0.425
Expected	[20.2]	[3.4]	[4.5]	[2.5]	[1.4]	[0.8]	[0.4]	[33.2]		
Total leukemia										
Observed	345	66	86	52	36	20	11	616	0.40 (–0.41; 1.51)	0.230
Expected	[342.4]	[67.7]	[87.9]	[49.5]	[31.7]	[17.9]	[9.7]	[606.7]		
Non-CLL										
Observed	226	34	49	28	23	12	8	380	1.38 (0.04; 3.34)	0.044
Expected	[219.8]	[37.9]	[48.2]	[27.0]	[16.6]	[9.0]	[4.7]	[363.2]		
Myeloid leukemia[d]										
Observed	169	24	35	18	19	10	7	282	1.85 (0.24; 4.28)	0.025
Expected	[159.8]	[27.9]	[35.5]	[20.0]	[12.3]	[6.6]	[3.4]	[265.5]		
Lymphatic leukemia[e]										
Observed	154	39	48	29	15	9	3	297	–0.59 (<–0.60; 0.30)	0.893
Expected	[160.5]	[36.1]	[47.3]	[26.7]	[17.9]	[10.5]	[6.0]	[305.0]		

[a] The expected number of deaths is the estimated number of background cases using the Poisson regression model in the absence of occupational radiation exposure.
[b] ERR/Sv estimates are calculated from a linear ERR model that contains background adjustments for age, calendar time, industrial status and first employer.
[c] *P* value represents a one-sided test of the linear ERR/Sv parameter.
[d] The myeloid leukemia disease group consists of all events in AML, CML and other myeloid groupings.
[e] The lymphatic leukemia disease group consists of all events in ALL, CLL and other lymphatic groupings.

is not surprising that the leukemia subtype results for male and female workers combined was not materially different from that for male workers alone (Supplementary Table S4; https://doi.org/10.1667/RR15358.1.S1). Supplementary analyses based on a multiplicative relative risk model also showed little evidence of a difference in the relative risk, associated with dose, between the genders ($P = 0.15$; Supplementary Table S5).

The potential effect of internal exposures on the risk estimates was examined by excluding workers flagged as monitored for internal exposures from the analysis. This resulted in non-CLL estimates that were consistent with the overall estimates [ERR = 1.66 (90% CI: <0; 5.62)], although less precise.

Although increased non-CLL ERR estimates were observed in the full analysis, the point estimate of ERR did decrease when follow-up in this cohort was successively extended (Table 4); the point estimates of ERR decreased by 44% with extended follow-up from 1996 to 2011. This pattern was observed not only in the main analysis but also in the analysis looking at mortality and incidence alone, where the ERR estimates similarly fell by 53% and 39%, respectively. This pattern may be partly explained by the variation in ERR point estimates by time since first exposure (Table 4), which shows some evidence ($P = 0.053$) that increased risks in relationship to dose were observed only in the first 40 years after follow-up and more specifically in the time period of 20–39 years after first exposure [ERR = 3.95 (90% CI: 1.36; 7.67)].

TABLE 4
Male Non-CLL, Variation in Linear ERR/Sv Estimates over Follow-up

	Main analysis[a]		Mortality only		Incidence only[a]	
	N	ERR/Sv (90% CI)	N	ERR/Sv (90% CI)	N	ERR/Sv (90% CI)
Overall[b]	380	1.38 (0.04; 3.34)	269	1.00 (–0.23; 2.90)	333	1.57 (0.11; 3.75)
Truncating follow-up to:						
12/31/2011	380	1.38 (0.04; 3.34)	269	1.00 (–0.23; 2.90)	333	1.57 (0.11; 3.75)
12/31/2006	315	1.84 (0.30; 4.13)	226	1.27 (–0.10; 3.41)	275	1.93 (0.30; 4.40)
12/31/2001	238	2.04 (0.28; 4.77)	171	1.95 (0.13; 4.90)	204	1.98 (0.19; 4.87)
12/31/1996	173	2.48 (0.33; 5.98)	134	2.12 (–0.10; 5.90)	140	2.59 (0.28; 6.59)
12/31/1991	126	1.20 (–0.60; 4.49)	103	1.74 (–0.14; 5.68)	96	1.25 (<0; 5.07)
Time since first exposure (years)						
0–19	124	0.66 (<0; 6.51)	96	<0 (<0; 3.54)	107	2.21 (<0; 10.18)
20–39	198	3.95 (1.36; 7.67)	128	2.45 (0.25; 5.88)	185	3.62 (1.07; 7.42)
40+	58	–0.28 (<0; 1.51)	62	0.32 (<0; 2.77)	60	–0.10 (<0; 1.96)
Test for heterogeneity[c]		$P = 0.053$		$P = 0.13$		$P = 0.13$

[a] In the main and incidence analysis, a small number of leukemia events occurring after first cancer registration (excluding non-melanoma skin cancers) are ignored, since follow-up is truncated at the date of first cancer event.

[b] For the overall results the ERR/Sv estimates are calculated from a linear ERR model that contains background adjustments for age, calendar time, gender, industrial status and first employer.

[c] Test for heterogeneity based on the likelihood ratio test comparing the overall model with models that allow the ERR to vary by time since first exposure.

Temporal Variation in ERR and EAR Estimates

When fitting a linear EAR model without attained age effect modification there was evidence of increased risk in relationship to external dose for non-CLL [EAR = 1.33 (90% CI: 0.04; 2.89)] (Table 5). Neither the ERR nor EAR models showed significant effect modification with attained age ($P = 0.10$ and $P = 0.14$, respectively), but both showed a similar pattern of larger point estimates of risk at lower and higher ages and smaller in risk at middle ages (40 to 69 years).

TABLE 5
Male Non-CLL, Temporal Variation in Linear ERR/Sv and EAR Estimates by Attained Age, Age at Exposure, Time since Exposure and Using Differing Lagging Strategies

	N	ERR model ERR/Sv (90% CI)	EAR model EAR × 10^4 Py-Sv (90% CI)
Overall[a]	380	1.38 (0.08; 3.24)	1.33 (0.04; 2.89)
Attained age (years)			
<40	47	15.20 (2.14; 37.73)	3.26 (0.48; 7.48)
40–69	206	0.42 (<0; 2.65)	0.40 (<0; 2.06)
70+	127	1.85 (0.12; 4.34)	5.36 (0.03; 12.31)
Test for heterogeneity[b]		$P = 0.10$	$P = 0.14$
Age when doses received (years)			
<30		6.21 (–0.57; 17.27)	3.99 (0.71; 8.32)
30–50		–0.39 (<0; 1.77)	–0.20 (<0; 1.55)
50+		2.58 (0.11; 6.14)	2.89 (<0; 9.02)
Test for heterogeneity[c]		$P = 0.24$	$P = 0.23$
Time since doses received			
2–24 years ago		2.28 (0.11; 5.35)	1.23 (–0.11; 2.97)
25+ years ago		0.37 (<0; 2.98)	1.82 (<0; 7.05)
Test for heterogeneity[d]		$P = 0.37$	$P > 0.50$
Alternative lagging strategies			
Lag time:			
10 years		1.25 (–0.18; 3.40)	1.80 (0.04; 3.95)
20 years		1.41 (–0.34; 4.20)	2.87 (–0.34; 6.71)
25 years		0.39 (<0; 3.11)	2.45 (<0; 7.70)
30 years		–0.23 (<0; 2.53)	1.82 (<0; 9.24)

[a] The overall models are based on using two-year doses, but the ERR/Sv estimates are very slightly different from those presented in previous tables, since findings are based on a parametric rather than stratified non-parametric background model.

[b] Test for heterogeneity based on the likelihood ratio test comparing the overall model with models that allow the ERR to vary attained age.

[c] Test for heterogeneity based on the likelihood ratio test comparing the overall model using two-year lag cumulative doses with models that partition the two-year lagged dose into three time windows based on the age at which the dose was received.

[d] Test for heterogeneity based on the likelihood ratio test comparing the overall model using two-year lag cumulative doses with models that partition the two-year lagged dose into two time windows based on the time since the dose was received.

There was no evidence of a difference in radiation-related risk for non-CLL by the age at which the dose was received, although there was a general pattern in which the point estimate of ERR and EAR associated with the dose received before age 30 and after age 50 years was higher than those associated with doses received between the ages of 30 and 49 years (Table 5). When alternative lagging strategies were considered, there was little difference between 2-, 10- and 20-year lagged results for both ERR and EAR estimates for non-CLL. However, slight differences in pattern were evident between ERR and EAR estimates when looking at longer lags, with the EAR estimate remaining relative consistent but the ERR point estimate declining at 25- and 30-year lag. This pattern was consistent with the results of the time-since-exposure analysis, which suggested that doses received more that 25 years previously may play a less important role when using the ERR model than when using the EAR model. The power to detect these variations in risks over time is low, and even when the ERR model is used, there is little evidence of variation in risk with time since the dose was received ($P = 0.37$) and such a pattern could just as well be explained by chance.

DISCUSSION

As with previously reported NRRW-3 analyses (*15*) there was no evidence of increased leukemia rates in the cohort compared to the national population, and the non-CLL mortality rate was lower than that observed nationally. Such findings are consistent with the healthy worker effect (HWE) (*23*) in which working populations tend to have lower disease rates than equivalent comparison national or regional populations. Any HWE is reasonably small in this cohort (non-CLL: SMR = 89) and any reduction in relationship to national rates is limited to mortality with no evidence of lowered rates for leukemia incidence (non-CLL: SIR = 98).

Although it may be instructive to examine the rates of leukemia in relationship to a national comparison group, the main interest in this study was to examine whether the rates of leukemia varied with the level of occupational external radiation exposure. We observed a positive association between cumulative dose of external radiation and the incidence of non-CLL among male workers. This association was largely driven by increased rates of myeloid leukemia with a large positive association observed for CML. ALL and unspecified leukemia were the only other subtypes to show positive, although highly imprecise, point estimates of risk.

One of the motivations behind this study was to derive radiation risk estimates with greater statistical precision than in the previously published NRRW-3 study (*14*) by using extended follow-up information. It is clear when the risks derived for this study [ERR = 1.38 (90% CI: 0.04; 3.34)] are compared with the previous results [ERR = 1.78 (90% CI: 0.17; 4.36)] that the precision of the estimates has increased markedly due to the increased maturity of the cohort, with the total number of leukemia events having increased by 72% (non-CLL from 224 to 402 events). Any increase in precision with increased follow-up needs to be balanced carefully against any dilution in risk that may occur if the risk decreases with time since exposure or attained age. There is only limited evidence that risk decreased with time since exposure ($P = 0.37$) or attained age ($P = 0.10$), but this may well tell us more about the limited power in this study to currently examine these effects than any lack of effect. The pattern of the point estimates of risk are suggestive of a dilution of risks associated with doses received many years previously, and the observed reduction in the magnitude of the linear ERR with increased follow-up may well partly be an artefact of this effect.

The central estimates of ERR and EAR obtained in this study for non-CLL are consistent with the latest incidence estimates derived from the LSS of Japanese atomic bomb survivors (*2*). [ERR = 1.74 at 1 Gy (90% CI: 0.79; 2.68), based on a linear-quadratic model. EAR = 2.14 at 1 Gy (90% CI: 1.20; 3.09), for males based on a linear-quadratic model]. Despite these consistencies, generalizing radiation risk estimates based on the LSS cohort compared to other populations is complicated by the fact that LSS cohort members had a single acute exposure, in contrast to the protracted chronic low-dose-rate exposures seen in nuclear workers. The shape of the dose response also shows some differences between the cohorts, with risk in this study best described by a linear function of dose with little evidence of the non-linearity ($P > 0.5$) observed in the LSS cohort.

Similarly, there were also differences in the temporal variation in risk between the cohorts that are worthy of further consideration. For example, the effect of attained age, time since exposure and age at exposure, and the temporal variation in risk over follow-up showed some differences between the cohorts.

The lack of a quadratic effect may partially be explained by the absence of information at higher doses (>500 mSv) in the NRRW cohort. However, at lower dose ranges the differences in predicted excess risk between the linear and linear-quadratic model are marginal. In the LSS cohort there was evidence of effect modification in relationship to attained age and time since exposure when the ERR model was used, and attained age and age at exposure when the EAR model was used. Models examining similar effects in the NRRW cohort are limited by low power due to lower doses and the number of cases (an estimated 17 excess cases of non-CLL compared to 94 in the LSS cohort). In general, the point estimates observed showed no consistent decrease in excess risks in relationship to attained age, as observed in the LSS cohort, and no consistent increase in risk in relationship to age at exposure.

One notable feature of both the LSS cohort and the Mayak workers in Russia (*24*) was an immediate increase in leukemia risk in the first five years after exposure followed by a subsequent decrease in excess risk over time, although

a smaller excess risk was still found to persist many years after exposure. Given this pattern, one might expect to observe an increased excess risk with the use of shorter lag periods in the analysis; however, this was not the case in the NRRW cohort in which risks were only found to decrease when lags of more than 20 years were used. This result is more consistent with a recently published study looking at temporal effects in the INWORKS cohort (*25*), in which excess leukemia risks were not observed in the first years after exposure, and the optimal lag period was 19 years. The temporal variation in risk within the NRRW cohort falls somewhere between these two options, with excess risks consistent across lag periods up to 20 years and with lower point estimates of ERR associated with doses received more than 25 years ago.

This pattern of risks tallies well with the time-since-first-exposure analysis, which showed an attenuation in risks 40 years after first exposure, with no evidence of increased risks. This finding is somewhat in conflict with the LSS cohort where small excess risks were found to persist more than 40 years after exposure for non-CLL. In the NRRW cohort this results in an attenuation of the central estimate of risk when the end of follow-up is moved from 2001 to 2011. While this may be the consequence of a genuine lack of long-term effect on leukemia it should also be noted that the average dose of the cohort has decreased markedly over time, and it may be difficult to detect small excess risks at these lower dose levels.

We noted differences between our results and those of the LSS and Mayak cohorts (*24*) [ERR/Gy = 4.98 (90% CI: 1.98; 13.74), male workers]. However, both the LSS cohort (single acute exposure, mean dose 0.1 Gy) and Mayak workers (chronic exposure with a mean dose of 0.39 Gy) had very different exposures compared to the NRRW cohort, in which workers generally had chronic low external dose exposures over a working lifetime with a mean dose of 0.025 Sv. Positive associations between non-CLL and external radiation exposure have also been found in other cohorts, including the INWORKS cohort (*26*) [ERR/Gy = 2.96 (90% CI: 1.17; 5.21)], the pooled French [ERR/Sv = 3.96 (90% CI: <0; 16.82)] and U.S. [ERR/Sv = 1.7 (90% CI: –0.22; 4.7)] nuclear worker cohorts (*27, 28*), as well as the residents living near the Techa river (*29*) [ERR/Gy = 4.9 (95% CI: 1.6; 14.3)] who were exposed to radioactive discharges from the Mayak plant. A meta-analysis of leukemia risks in relationship to cohorts exposed to chronic low-dose exposures (*30*), which included these cohorts as well as others where no leukemia excess risk was detected, found a preferred pooled estimate of non-CLL risk [ERR = 1.9 (95% CI: 0.7; 3.2)] that was consistent with the estimate from this study.

Some caution is needed when comparing results between studies, since some have used recorded doses or dose equivalents, e.g., this study, previous NRRW analyses, pooled French and U.S. cohorts, while others have used absorbed organ doses to the red bone marrow, e.g., the INWORKS and LSS cohort studies. In general, dose equivalents can be viewed as conservative estimates of external dose to the deep tissue organs that take no account of shielding factors from other tissues. The net effect is that organ dose estimates tend to be somewhat attenuated when compared with dose equivalents. Therefore, where a positive association exists with radiation exposure, the point estimates of ERR calculated using dose equivalents are likely to be attenuated when compared to using absorbed organ doses. For example, in the INWORKS cancer study (*13*) point estimates of solid cancer risk where attenuated when using recorded doses [ERR = 0.33 (90% CI: 0.12; 0.56)] compared to absorbed colon doses [ERR = 0.47 (90% CI: 0.18; 0.79)]. This may partially explain why the non-CLL point estimates of ERR are somewhat reduced (although statistically compatible) when compared with estimates from the studies that use absorbed organ doses, although it is important to note that there is no gain in the precision of risk estimates by the choice of dose metric (in terms of model fit).

Much of the excess risk that we observed for non-CLL was driven by an increased risk for CML [ERR = 6.77 (90% CI: 2.13; 15.44)].This increased rate of CML was also found in a previous analysis of this cohort and in other studies such as the WISMUT cohort of uranium miners (*31*) [ERR = 7.20 (95% CI: 4.48; 19.65)] and the INWORKS cohort [ERR = 10.45 (90% CI: 4.48; 19.65)], which includes a subset of the NRRW-3 cohort. However, the higher-dose LSS and Mayak studies, which both show increased risks for CML, also showed excess risks that were just as high for AML if not higher than for CML. There was no evidence of increased risk for CLL in this cohort and this is in general agreement with the prevailing scientific view that radiation has little effect on CLL rates. Several studies have suggested a possible link between radiation exposure and CLL rates (*32–35*) but that was not found in this study.

A particular strength of this study is that we were able to calculate risks using both mortality and incidence data. Outcome misclassification for leukemia and subtypes of leukemia is a potential limitation of any mortality study, since the specificity on death certificates is less precise and can induce bias particularly in subtype analyses. In this context it may be worth noting that point estimates of non-CLL risks were somewhat attenuated when analyses were based on mortality data alone [ERR = 1.00 (90% CI: –0.23; 2.90)].

One limitation of this study, common to most occupational studies, was the absence of information on potential confounders that are known to be risk factors for the disease under study. However, for leukemia the number of potential confounders is limited and the association between the potential confounders and level of external dose would have to be strong to cause much effect, especially having already adjusted for several other baseline factors including industrial status. Smoking is one potential confounder for myeloid leukemia (*36*), but the association is not strong, and

it is known from the lung cancer and chronic obstructive pulmonary disease risks already published on this cohort that smoking is unlikely to have a positive confounding effect in this study (*18*).

A number of chemicals are also known to be associated with increased leukemia risk (*37*); however, exposure of workers to such chemicals in the nuclear industry is likely to be small, although some potential bias from this unmeasured confounder on study results cannot be ruled out. A chemical of particular interest is benzene, which in a recent review (*38*) was found to be more clearly and strongly related to AML than CML. As the main evidence of increased risks in this study comes for CML rather than AML, this suggests that benzene is unlikely to be a strong confounding factor in this study.

In this same review (*38*), an association was found between benzene exposure and myelodysplastic syndromes (MDS), which are commonly considered to be a preleukemic condition; up to one third of cases go on to develop AML (*37*). MDS have also been linked to higher doses of radiation in studies of both the Nagasaki atomic bomb survivors and patients receiving radiotherapy (*39*). Unfortunately MDS have only really been identifiable as a separate condition since the implementation of ICD-10 (*40*), which was from 1995 for cancer incidence, and from 2001 for mortality in the NRRW cohort. MDS are not included in the definition of leukemia events used in the main analysis; however, a sub-analysis of MDS, when restricting analysis to the ICD-10 follow-up period, did not reveal any evidence of an association with radiation exposure [ERR = –0.36 (90% CI: <0; 2.17), 140 cases]. The MDS ERR estimate is very similar in magnitude to that observed for AML [ERR = –0.28 (90% CI: <0; 2.08), 189 cases], which adds to the evidence that benzene exposure is not likely to greatly confound risk estimates in this study.

As mentioned in the analysis of cancer of this cohort (*18*) another possible source of bias in the analysis results is the potential effect of both measured and unmeasured neutron doses on risk estimates. Measurements from early neutron dosimeters were relatively poor compared to data from contemporary devices (*41*). Furthermore, sources of neutrons and monitoring practices varied widely among facilities over time. Thus, neutron exposure data are likely to be incomplete and some exposure misclassification is unavoidable in this study. Although neutron exposures are likely to be small in relationship to those from photons (*42*), additional research is needed to understand the effects of neutrons in this study and in other studies of populations exposed to mixed radiation fields.

A number of workers in this cohort were also potentially exposed to internal radionuclides during employment, predominately from uranium and plutonium exposures. In most occupational settings exposure to internal radionuclides (and in particular, plutonium and uranium) are low compared to external exposures (*43–46*) and studies that have directly adjusted for the effects of estimated plutonium doses have shown little effect on the leukemia risk estimates associated with external dose (*47, 48*). Unfortunately, internal dose assessments are not currently routinely available for the cohort; however, supplementary analyses found no evidence of a difference in ERR estimates between workers monitored and not monitored for internal exposures ($P = 0.28$). This finding tallies with the expectation that internal doses will generally be low in this cohort and suggests that the confounding effect of internal exposures may not be large for leukemia end points.

In summary, much of the evidence for setting radiation protection standards is based on extrapolation of risks from high-dose or acute radiation studies. The current study provides further direct evidence that non-CLL may be increased by low-dose and low-dose-rate radiation exposure. The risks are generally consistent with those observed in the atomic bomb survivor studies and consistent with risks coefficients on which international radiation safety standards, including the dose limits and constraints used to control exposures, are based. While there was some indication of temporal variation in leukemia risk that is different from those derived of the LSS cohort, the power to detect such effects is limited. Further follow-up of this or other cohorts incorporating further follow-up may be useful in this regard.

SUPPLEMENTARY INFORMATION

Table S1. Leukemia subtype disease group definitions.

Table S2. Male standardized mortality and incidence ratios (SMR/SIRs) by leukemia subtype.

Table S3. Female standardized mortality and incidence ratios (SMR/SIRs) by leukemia subtype.

Table S4. Combined male and female leukemia incidence in relationship to external radiation dose: ERR/Sv estimates, observed and expected number of leukemia cases from the Poisson regression analysis.

Table S5. Non-CLL, variation in relative risk per Sv (RR/Sv) by gender.

ACKNOWLEDGMENTS

We thank all the organizations and individuals participating in the NRRW for their cooperation and support. We also gratefully acknowledge the help of Tina Wilcock and Mary Philipson for data management support throughout the course of project. The findings and conclusions in this work are those of the authors and do not necessarily represent the views of Public Health England.

Received: February 4, 2019; accepted: July 28, 2019; published online: August 26, 2019

REFERENCES

1. Folley JH, Borges W, Yamawaki T. Incidence of leukemia in survivors of the atomic bomb in Hiroshima and Nagasaki, Japan. Am J Med 1952; 13:311–21.
2. Hsu WL, Preston DL, Soda M, Sugiyama H, Funamoto S, Kodama K, et al. The incidence of leukemia, lymphoma and multiple

myeloma among atomic bomb survivors: 1950–2001. Radiat Res 2013; 179:361–82.

3. Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950–1997. Radiat Res 2003; 160:381–407.
4. Richardson D, Sugiyama H, Nishi N, Sakata R, Shimizu Y, Grant EJ, et al. Ionizing radiation and leukemia mortality among Japanese atomic bomb survivors, 1950–2000. Radiat Res 2009; 172:368–82.
5. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103. Ann ICRP 2007; 37:1–332.
6. Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, et al. Studies of the mortality of atomic bomb survivors, Report 14, 1950–2003: an overview of cancer and noncancer diseases. Radiat Res 2012; 177:229–43.
7. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, et al. Solid cancer incidence in atomic bomb survivors: 1958–1998. Radiat Res 2007; 168:1–64.
8. United Nations Scientific Committee on the Effects of Atomic Radiation. Effects of ionizing radiation. UNSCEAR 2006 Report, Volume 1. New York: United Nations; 2008.
9. Health risks from exposure to low levels of ionizing radiation: BEIR VII Phase 2. Washington, DC: The National Academies Press; 2006.
10. Preston DL, Kusumi S, Tomonaga M, Izumi S, Ron E, Kuramoto A, et al. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950–1987. Radiat Res 1994; 137:S68–97.
11. Cardis E, Gilbert ES, Carpenter L, Howe G, Kato I, Armstrong BK, et al. Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. Radiat Res 1995; 142:117–32.
12. Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, et al. The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: estimates of radiation-related cancer risks. Radiat Res 2007; 167:396–416.
13. Richardson DB, Cardis E, Daniels RD, Gillies M, O'Hagan JA, Hamra GB, et al. Risk of cancer from occupational exposure to ionising radiation: retrospective cohort study of workers in France, the United Kingdom, and the United States (INWORKS). BMJ 2015; 351:h5359.
14. Muirhead CR, O'Hagan JA, Haylock RG, Phillipson MA, Willcock T, Berridge GL, et al. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. Br J Cancer 2009; 100:206–12.
15. Muirhead CR, O'Hagan JA, Haylock RG, Phillipson MA, Willcock T, Berridge GL, et al. HPA-RPD-062 - Third analysis of the National Registry for Radiation Workers: Occupational exposure to ionising radiation in relation to mortality and cancer incidence. Didcot, UK: Health Protection Agency, Centre for Radiation, Chemical and Environmental Hazards; 2009.
16. Kendall GM, Muirhead CR, MacGibbon BH, O'Hagan JA, Conquest AJ, Goodill AA, et al. Mortality and occupational exposure to radiation: first analysis of the National Registry for Radiation Workers. BMJ 1992; 304:220–5.
17. Muirhead CR, Goodill AA, Haylock RG, Vokes J, Little MP, Jackson DA, et al. Occupational radiation exposure and mortality: second analysis of the National Registry for Radiation Workers. J Radiol Prot 1999; 19:3–26.
18. Haylock RGE, Gillies M, Hunter N, Zhang W, Phillipson M. Cancer mortality and incidence following external occupational radiation exposure: an update of the 3rd analysis of the UK national registry for radiation workers. Br J Cancer 2018; 119:631–7.
19. Muirhead CR, Goodill AA, Haylock RG, Vokes J, Little MP, Jackson DA, et al. Second analysis of the National Registry for Radiation Workers: Occupational exposure to ionizing radiation and mortality. NRPB Report R307. London: HMSO; 1999.
20. Zhang W, Haylock RGE, Gillies M, Hunter N. Mortality from heart diseases following occupational radiation exposure: analysis of the National Registry for Radiation Workers (NRRW) in the United Kingdom. J Radiol Prot 2019; 39:327–53.
21. 20th Century mortality - 100 years of mortality data in England and Wales by age, sex, year and underlying cause. CD-ROM (with updates). London: Office for National Statistics; 2004.
22. Preston DL, Lubin JH, Pierce DA, McConney ME, Shilnikova NS. EPICURE version 2 user guide. Ottawa, Canada: Risk Sciences International; 2015.
23. Wen CP, Tsai SP, Gibson RL. Anatomy of the healthy worker effect: a critical review. J Occup Med 1983; 25:283–9.
24. Kuznetsova IS, Labutina EV, Hunter N. Radiation risks of leukemia, lymphoma and multiple myeloma incidence in the Mayak cohort: 1948–2004. PLoS One 2016; 11:e0162710.
25. Daniels RD, Bertke SJ, Richardson DB, Cardis E, Gillies M, O'Hagan JA, et al. Examining temporal effects on cancer risk in the international nuclear workers' study. Int J Cancer 2017; 140:1260–9.
26. Leuraud K, Richardson DB, Cardis E, Daniels RD, Gillies M, O'Hagan JA, et al. Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study. Lancet Haematol 2015; 2:e276–81.
27. Schubauer-Berigan MK, Daniels RD, Bertke SJ, Tseng CY, Richardson DB. Cancer mortality through 2005 among a pooled cohort of U.S. nuclear workers exposed to external ionizing radiation. Radiat Res 2015; 183:620–31.
28. Metz-Flamant C, Laurent O, Samson E, Caer-Lorho S, Acker A, Hubert D, et al. Mortality associated with chronic external radiation exposure in the French combined cohort of nuclear workers. Occup Environ Med 2013; 70:630–8.
29. Krestinina L, Preston DL, Davis FG, Epifanova S, Ostroumova E, Ron E, et al. Leukemia incidence among people exposed to chronic radiation from the contaminated Techa River, 1953–2005. Radiat Environ Biophys 2010; 49:195–201.
30. Daniels RD, Schubauer-Berigan MK. A meta-analysis of leukaemia risk from protracted exposure to low-dose gamma radiation. Occup Environ Med 2011; 68:457–64.
31. Kreuzer M, Sobotzki C, Fenske N, Marsh JW, Schnelzer M. Leukaemia mortality and low-dose ionising radiation in the WISMUT uranium miner cohort (1946–2013). Occup Environ Med 2017; 74:252–8.
32. Richardson DB, Wing S, Schroeder J, Schmitz-Feuerhake I, Hoffmann W. Ionizing radiation and chronic lymphocytic leukemia. Environ Health Perspect 2005; 113:1–5.
33. Rericha V, Kulich M, Rericha R, Shore DL, Sandler DP. Incidence of leukemia, lymphoma, and multiple myeloma in Czech uranium miners: a case-cohort study. Environ Health Perspect 2006; 114:818–22.
34. Romanenko AY, Finch SC, Hatch M, Lubin JH, Bebeshko VG, Bazyka DA, et al. The Ukrainian-American study of leukemia and related disorders among Chornobyl cleanup workers from Ukraine: III. Radiation risks. Radiat Res 2008; 170:711–20.
35. Linet MS, Schubauer-Berigan MK, Weisenburger DD, Richardson DB, Landgren O, Blair A, et al. Chronic lymphocytic leukaemia: an overview of aetiology in light of recent developments in classification and pathogenesis. Br J Haematol 2007; 139:672–86.
36. Cogliano VJ, Baan R, Straif K, Grosse Y, Lauby-Secretan B, El Ghissassi F, et al. Preventable exposures associated with human cancers. J Natl Cancer Inst 2011; 103:1827–39.
37. Eastmond DA, Keshava N, Sonawane B. Lymphohematopoietic cancers induced by chemicals and other agents and their

implications for risk evaluation: An overview. Mutat Res Rev Mutat Res 2014; Epub ahead of print.

38. Benzene. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 120. Lyon, France: International Agency for Research on Cancer; 2018.

39. Iwanaga M, Hsu WL, Soda M, Takasaki Y, Tawara M, Joh T, et al. Risk of myelodysplastic syndromes in people exposed to ionizing radiation: a retrospective cohort study of Nagasaki atomic bomb survivors. J Clin Oncol 2011; 29:428–34.

40. ICD-10. International statistical classification of diseases and related health problems. Geneva: World Health Organization; 1990.

41. Kite A, Anderson R. An overview of retrospective occupational dosimetry at BNFL. Proceedings, IRPA9: 1996 International Congress on Radiation Protection proceedings. Ninth International Congress of the International Radiation Protection Association. April 14–19, 1996, Vienna, Austria. 1996. France: IRPA; 1996. p. 3-102–5. (https://bit.ly/2OInOuZ)

42. Gillies M, Richardson DB, Cardis E, Daniels RD, O'Hagan JA, Haylock R, et al. Mortality from circulatory diseases and other non-cancer outcomes among nuclear workers in France, the United Kingdom and the United States (INWORKS). Radiat Res 2017; 188:276–90.

43. Daniels RD, Lodwick CJ, Schubauer-Berigan MK, Spitz HB. Assessment of plutonium exposures for an epidemiological study of US nuclear workers. Radiat Prot Dosimetry 2006; 118:43–55.

44. Omar RZ, Barber JA, Smith PG. Cancer mortality and morbidity among plutonium workers at the Sellafield plant of British Nuclear Fuels. Br J Cancer 1999; 79:1288–301.

45. Yiin JH, Anderson JL, Daniels RD, Bertke SJ, Fleming DA, Tollerud DJ, et al. Mortality in a combined cohort of uranium enrichment workers. Am J Ind Med 2017; 60:96–108.

46. Silver SR, Bertke SJ, Hein MJ, Daniels RD, Fleming DA, Anderson JL, et al. Mortality and ionising radiation exposures among workers employed at the Fernald Feed Materials Production Center (1951–1985). Occup Environ Med 2013; 70:453–63.

47. Daniels RD, Bertke S, Waters KM, Schubauer-Berigan MK. Risk of leukaemia mortality from exposure to ionising radiation in US nuclear workers: a pooled case-control study. Occup Environ Med 2013; 70:41–8.

48. Schubauer-Berigan MK, Daniels RD, Fleming DA, Markey AM, Couch JR, Ahrenholz SH, et al. Chronic lymphocytic leukaemia and radiation: findings among workers at five US nuclear facilities and a review of the recent literature. Br J Haematol 2007; 139:799–808.