Radiation risks of lymphoma and multiple myeloma incidence in the updated NRRW-3 cohort in the UK: 1955–2011

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Abstract
The effect of external radiation on lymphoma, including non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL) and multiple myeloma (MM) incidence was evaluated in the National Registry for Radiation Workers based upon the third analysis cohort but with an additional 10 years of follow-up. The study includes 172 452 workers, of whom (90%) were men with 5.25 million person-years of follow-up from 1955 through to the end of 2011. A total of 711 cases of NHL, 113 cases of HL and 279 cases of MM were registered. Poisson regression was used to estimate the excess relative risk per unit of cumulative exposure to ionising radiation. A statistically significant association was found between radiation dose and the incidence of NHL and MM. There was no evidence of radiation associated excess risk for HL. The reported associations are based on a very small proportion of exposed workers, in particular among workers with cumulative doses above 0.5 Sv so should be treated with caution, further investigations are necessary to confirm our results.

1. Introduction

Lymphoma is a cancer that originates in the lymph glands or other organs of the lymphatic system. There are two main types namely non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). HL is characterised by the presence, under a microscope, of Reed Sternberg cells. Reed Sternberg cells are a type of white blood cell called a B lymphocyte (normally make antibodies to help fight infections) that has become cancerous. HL is rare and around 2100 people are diagnosed in the UK each year. In contrast, NHL which does not involve Reed Sternberg cells is more common with around 13 700 cases diagnosed each year in the UK (Cancer Research UK). This makes it the sixth most common type of cancer in adults. NHL Incidence increases with age; 35% of people diagnosed with NHL are aged 75 and over and is slightly more common in men than in women. Although some studies have suggested that chemicals such as benzene and certain herbicides and insecticides (weed- and insect-killing substances) and radiation exposure may be linked to an increased risk of NHL, research to clarify these possible links is still in progress.

Multiple myeloma (MM) is a blood cancer arising from plasma cells that are a type of white blood cell made in the bone marrow. MM accounts for 15% of blood cancers, and 2% of all cancers. It mainly affects those over the age of 65, but it is occasionally diagnosed in people much younger and it is more common in men than women (Cancer Research UK). Multiple environmental factors are thought to increase the risk of developing MM, including exposure to certain types of industrial and agricultural chemicals and exposure to high doses of radiation, but the evidence is not clear.

The effects of radiation exposure on lymphatic cancers (NHL and HL) and MM have been studied widely among the Japanese A-bomb survivors, large groups of radiation workers and also among patients receiving radiotherapy and diagnostic irradiation (UNSCEAR 2008, Richardson et al 2009, Hsu et al 2013, Leuraud et al 2015, Kuznetsova et al 2016). Overall, the strength of the evidence from these studies was mixed.

The National Registry for Radiation Workers (NRRW) in the UK continues to be one of the most important sources providing information on health effects related to the long-term radiation exposure from low dose external exposure, because it contains a very large group of workers with a wide variety of exposure...
the earliest of which have now been followed up for more than 60 years. The recent updated NRRW-3 cohort has been used to estimate risks of cancer mortality and incidence, non-cancer mortality and the risk of leukaemia in relation to external exposure with follow-up extended by 10 years (Haylock et al 2018, Gillies et al 2019, Zhang et al 2019). These analyses provide the most precise estimates up to date of the risks of cancer and non-cancer mortality and cancer incidence following occupational external radiation exposure and strengthens the evidence for raised risks due to these exposures. This study also uses the updated NRRW-3 cohort data to analyse radiation risk of MM and lymphatic cancer incidence in relation to external radiation exposure. In particular, we examine the shape of the dose–response relationship and assess any temporal variation in radiation risk with attained age, age at exposure and time since exposure.

2. Materials and methods

2.1. The study cohort and follow-up

The cohort included in this analysis is essentially the same as that reported previously (Muirhead et al 2009a, 2009b, Haylock et al 2018), although there are a number of small differences mainly due to changes in follow-up information over time and the inclusion of ten additional years of dosimetry information. The analysis cohort consists of 172 452 workers and of these only about 10% were female workers. Detailed information about the definition of the study population, cohort design, data collection, the characteristics of the workers and follow-up procedures for this updated NRRW-3 cohort are given in the earlier publications (Muirhead et al 2009a, 2009b, Haylock et al 2018). Briefly, the NRRW in the UK was set-up in 1976 and includes workers from a wide range of employer organisations. These include most of the nuclear industry in the UK; British Nuclear Fuels Ltd (BNFL), the United Kingdom Atomic Energy Authority (UKAEA), the Atomic Weapons Establishment, British Energy Generation and Magnox Electric sites in England and Wales and Scotland, the Ministry of Defence (MoD), GE Healthcare (formerly Amersham International) as well as many smaller organisations in the research and industrial sectors that are located in all parts of the UK.

The study population comprises workers from these organisations who were individually monitored for external radiation exposure and for whom individual dose records were kept. Data collected from employers consist of individual identifiers, factors such as date of birth, gender and industrial classification, and radiation dose histories. These data were audited prior to their inclusion in the analysis (Muirhead et al 2009a, 2009b). The NRRW cohort contains prospectively collected data about workers in employment since 1976 when the study began, but also retrospectively about radiation workers employed from the mid-1940s have been included in the analyses.

Information on cancer registrations, mortality and emigrations for worker resident in England and Wales was obtained from the National Health Service Central Registers via NHS Digital, while for Scottish residents these data were obtained from National Records of Scotland. For consistency with previous analyses the cause of death and cancer diagnoses were coded in accordance with the International Classification of Diseases, 9th revision (ICD-9), which was issued in 1977 (WHO 1977). Analyses were limited to first primary cancer diagnosed during the follow-up period among NRRW-3 cohort members unless the first cancer was a non-melanoma skin cancer.

Dose information received from employers based on annual external whole-body dose for each worker.

2.2. Radiation exposure

The external dose estimates used here were identical to those for NRRW-3 analyses; for each radiation worker, employers supplied us with an annual dose of whole-body penetrating radiation and most of the doses are associated with x-ray and gamma ray exposure and to a lesser extent beta particle and neutrons (Muirhead et al 2009a, 2009b, Haylock et al 2018). Dose to the surface of the body were monitored using individual film badges (or personal monitors) with adjustment for energy and angular dependence of the detector; they were calibrated as the operational quantities for the individual monitoring of external exposure were the personal dose equivalent at a tissue depth of 10 mm, H\textsubscript{p} (10), expressed as in Sv. As doses were recorded primarily to ensure compliance with dose limits or constraints, corrections were applied to arrive at more accurate dose estimates (Muirhead et al 2009a, 2009b).

The collective external dose for the study population, after applying dose corrections, was estimated to be 4348 person Sv. The mean cumulative unlagged dose was 24.9 mSv overall (27.0 mSv for men and 5.6 mSv for women) and varied considerably between employers; the highest mean cumulative doses arise for organisation using the PHE Personal Dosimetry Service (PDS, 54.2 mSv) and British Nuclear Fuel plc (BNFL, 53.6 mSv), followed by UKAEA (UKAEA, 34 mSv) and GE Healthcare, 31.4 mSv (Muirhead et al 2009a, 2009b). The main contributors to the collective external dose are BNFL, UKAEA, MoD and British Energy Generation and Magnox Electric (England and Wales). Of the total cohort, most workers were exposed to relatively low radiation doses; about two thirds of workers had a lifetime dose less than 10 mSv.
and 6% of workers had a lifetime dose more than 100 mSv; they contributed nearly 60% of the collective dose in the study population (Muirhead et al 2009a, 2009b, Haylock et al 2018). Individuals who worked in the early years of the UK nuclear programme received higher annual doses than in later years. The main contribution to the collective external dose came from those who started work in the 1950s (mean dose of 77.7 mSv). However, persons who started radiation work in the 1960s and 1970s also made a sizeable contribution to the collective dose with mean doses of 28.6 mSv and 22.9 mSv in each decade, respectively.

Some workers in this cohort were also potentially exposed to internal emitters (i.e. radionuclides which have been inhaled or ingested, such as plutonium, uranium and tritium). However, estimates of doses from internal emitters were not generally available for the NRRW cohort. Information was available as to whether a worker was ever monitored for internal exposure (i.e. a two-level categorical variable: monitored and unmonitored). Of the updated NRRW-3 cohort, about 25% of workers were monitored for potential exposure to internal emitters. In addition, a substantial proportion of these workers accumulated higher external doses and majority were from BNFL Sellafield and tended to work longer. The external doses received by workers monitored for internal exposure (mean dose 61 mSv) were higher than those who were not monitored for internal exposure (mean dose 13 mSv).

2.3. Statistical methods

The statistical methods applied here were similar to those used previously in analyses of this cohort (Haylock et al 2018, Gillies et al 2019, Zhang et al 2019). Briefly, for each worker, person-years at risk were accumulated over time from the date of the start of follow-up for each worker began 10 years after the date of start radiation work with a participating employer or 1 January 1955, whichever occurred latest. As in previous NRRW analyses, the follow-up experience of workers prior to 1955 was excluded from the analysis because of indications that follow-up may be incomplete prior to this date (Muirhead et al 2009a, 2009b). The follow-up ended on the date of the first cancer registration, date of death, emigration, their 85th birthday or 31 December 2011 whichever occurred first. Tabulations of person years, cancer cases and summary variables were created using DATAB (Preston et al 2015). The categories of the tabulation included sex, attained age (15–19, 20–24, … 80–85), calendar year (1955–, 1960–, … 2010–2011), first employer (15 different employee), industrial classification (industrial/non-industrial/unknown), internal monitoring status categories (monitored for internal radiation/non-monitored) and the cumulative dose in eight categories (0–, 5–, 10–, 20–, 50–, 100–, 200–, 500+ mSv). Like previous NRRW analyses, cumulative exposures were also lagged by 10 years (y): the first 10 years of follow-up were excluded from analysis. This was to allow for a latency period between radiation exposure and disease onset and because a strong healthy worker effect is expected in the first years of employment.

Poisson regression was used to investigate the dependence of disease risk on radiation dose and was conducted by calculating relative risk (RR) or excess relative risk (ERR = RR−1) estimates. Analyses were initially based on a linear ERR model expressed as:

\[ b_0(1 + \beta \times \text{dose}). \]  

(equation (1)), where \(\beta\) is the linear exposure-response trend parameter, corresponding to the ERR per unit dose (Sv) and \(b_0\) (equation (2)) is the background incidence rate in the absence of radiation exposure and depends on various factors that can affect risk of cancer. In contrast to previous analyses here a parametric approach was taken for modelling the background disease rates and modelled as logarithms of the cancer rates. They were gender (\(\text{gen}\)), gender-specific linear and linear-quadratic and quadratic splines functions of the logarithm of attained age 60 years (age), birth cohort (b.year), industrial classification (indust.class) and male-specific first employer group (femp.grp). We did not use a female specific first employer group factor as it did not change the overall result for solid cancers. The background model is described as follows.

\[ b_0 = \exp \left[ \alpha_{\text{gen}} + \beta_{\text{gen}} \log \left( \frac{\text{age}}{60} \right) + \lambda_{\text{gen}} \log^2 \left( \frac{\text{age}}{60} \right) + \gamma_{\text{male}} \log^2 \left( \frac{\text{age}}{60} \right) I_{\text{age}>60} \right. \]

\[ + \ \text{gen} \times \text{indust.class} + \ \text{gen} \times \text{b.year} + \text{male} \times \text{femp.grp} \].

Deviations from the linear model (equation (1)) were evaluated by fitting two alternative models, a pure-quadratic model \((Q = b_0(1 + \beta \times \text{dose}^2))\) or the linear-quadratic model \((LQ = b_0(1 + \beta_1 \times \text{dose} + \beta_2 \times \text{dose}^2))\) and comparing the difference in fit. The Akaike information criterion (AIC) was used to select the best fitting model; if a model is more than two AIC value lower than another, then it is considered significantly better than that model (Burnham and Anderson 2004). To
examine how risks varied over the whole dose range, further analyses were carried out when restricting data to experience at cumulative doses less than <500, <200 and <100 mSv respectively.

Differences in the ERR/Sv were evaluated for several effect modifiers; sex, attained age, age at first exposure, time since first exposure, duration of exposure, industrial status and internal radiation monitoring. Differences in the ERR/Sv across levels of each modifying factors were assessed by comparing (equation (1)) with the model: $b_0(1 + \beta_j \times \text{dose})$, where $j$ denoted the number of the index of categories of the modifying factor.

Various subsidiary analyses were also conducted to assess whether the main findings were affected by various factors. In the absence of internal doses in the NRRW cohort, we investigated whether the tests for trends in risks of NHL and MM incidence with external radiation might have been influenced whether a person was monitored for internal radiation. Two approaches were taken, (a) excluding workers who were monitored for internal exposure and (b) adjusting the results based on whether or not a worker had ever internally monitored (using the two-level indicator internal exposure factor). In order to allow for a possible healthy worker survivor effect (HWSE), the data were adjusted for a two-level duration of employment factor by adding it to the baseline model (equation (2)). Two factors were considered, one where the cut point was at 10 years (i.e. <10 and 10 or more years) and a second where the cut point was at 30 years. The sensitivity of the findings to the choice of lag period was also examined and lag period 5, 15 and 20 years were used to investigate trends in risk with dose.

All the analyses here were carried out using the AMFIT module in the EPICURE (Preston et al 2015). Likelihood ratio tests and likelihood-based confidence intervals (CIs) were reported. The p-values reported here are primarily two-sided tests with 95% CIs.

3. Results

The current analysis comprises 172 452 workers, 90% of whom were men, from the NRRW who were followed up until the end of 2011 and accrued 5.25 million person-years. Only 12% of the workers had ever been employed by more than a single participating employer. The employer with most workers was the UK MOD with 37% of the cohort while 23% were employed by British Nuclear Fuels plc (BNFL) and 16% by UK Atomic Energy Authority (UKAEA). The mean duration of work at these organisations was between 5 and 15 year, and over half of the workers (61%) started their employment aged less than 30 year (average 30 year for males and 27 year for females). The follow-up period exceeded 25 years for 63% of the cohort members and 38% of workers were followed up to at least 65 of age.

By the end of 2011, a total of 824 cases of lymphomas were recorded of which 711 were NHL (ICD-9-code: 200, 202.1–202.3, 202.5–202.9), 113 were HL (ICD-9: 201) and 279 were MM (ICD-9: 203.0, 203.2–203.9) based on a 10 year lag period in the updated NRRW-3 cohort. The number of cases for each disease are slightly larger than reported in the recent update NRRW-3 study in which a few cases (four from NHL, three from HL and two from MM) were excluded because they occurred in uninformative baseline strata of the models used in that study (Haylock et al 2018). Virtually all lymphomas (95%) and MM cases (96%) were among males and 47% of the NHL, 38% of the HL and 45% of the MM cases were identified in the last 10 years of follow-up. More than half of the observed NHL and about 74% of the MMs occurred above 60 years of age, while 70% of the HL cases were diagnosed before age at 60. Among lymphomas and MM cases, only 27% and 31% of them respectively were among workers monitored for internal exposure and only four of the cases with lymphomas were among females monitored for internal exposure. There were no female cases of MM registered.

3.1. Lymphoma

The dose response relationships for NHL and HL were modelled separately and the results are shown in table 1 and figure 1. For NHL, over the full dose range, there was good evidence for both a linear model with an estimated ERR/Sv of 1.11 (95% CI: 0.02; 2.60, $p = 0.045$, AIC = 5141.0) and a pure-quadratic model with an estimated ERR at 1 Sv of 2.44 (95% CI: 0.22; 5.82, $p = 0.026$, AIC = 5140.1) over no dose response relationship. There was no evidence that a linear-quadratic model (AIC = 5142.1) fitted the data better than either the linear model ($p = 0.33$) or the pure-quadratic model ($p > 0.5$). This result is further confirmed by looking at the figure 1(a) which shows dose response for linear and pure-quadratic trends together with eight dose-category-specific RR estimates (table 1), the trend of this data is suited to for both linear and a pure-quadratic fit. However, much of the evidence for the dose response arose from a small number of cases (ten cases) among workers with lifetime doses exceeding 500 mSv, although their patterns of annual dose were not unusual i.e. no particularly high doses in any one year. Among these ten cases the majority (seven cases) were BNFL workers who were monitored for potential for internal exposure to plutonium and five of them worked more than 30 years.
**Table 1.** The relative risk (RR) estimated by dose category and excess relative risk (ERR) of lymphomas (non-Hodgkin lymphoma and Hodgkin lymphoma) and multiple myeloma in relation to ionising based on 10 year lag period.

| Cumulative dose (Sv) | Person-years of follow-up | Non-Hodgkin lymphoma | Hodgkin lymphoma | Multiple myeloma |
|----------------------|---------------------------|----------------------|------------------|------------------|
|                      |                           | No. | RR (95% CI)     | No. | RR (95% CI)     | No. | RR (95% CI)     |
| <0.005               | 1 914 568                 | 336 | 1               | 63  | 1               | 112 | 1               |
| 0.005+               | 498 886                   | 88  | 0.86 (0.67; 1.08)| 14  | 0.89 (0.47; 1.57)| 32  | 0.96 (0.63; 1.41)|
| 0.01+                | 360 044                   | 90  | 1.12 (0.88; 1.42)| 10  | 0.89 (0.42; 1.71)| 44  | 1.68 (1.16; 2.39)|
| 0.02+                | 393 847                   | 97  | 1.00 (0.78; 1.26)| 15  | 1.22 (0.64; 2.18)| 36  | 1.13 (0.75; 1.66)|
| 0.05+                | 194 251                   | 31  | 0.61 (0.41; 0.89)| 2   | 0.34 (0.06; 1.12)| 27  | 1.65 (1.04; 2.54)|
| 0.1+                 | 115 485                   | 33  | 1.06 (0.71; 1.52)| 7   | 1.95 (0.76; 4.34)| 13  | 1.34 (0.70; 2.35)|
| 0.2+                 | 67 390                    | 26  | 1.33 (0.85; 2.01)| 2   | 0.91 (0.00; 3.23)| 10  | 1.69 (0.80; 3.21)|
| 0.5+                 | 12 363                    | 10  | 2.34 (1.13; 4.32)| 0   | —               | 5   | 3.83 (1.29; 9.12)|
| Total no. (female)  | 3 556 834 (303 299)       | 711 (33) | 1.11 (0.02; 2.60)| 113(5) | −0.57 (<−1.78; 4.36)| 279 (10) | 2.63 (0.30; 6.37) |

**Bold:** statistical significance of $p < 0.05$. 

**ERR/Sv (95% CI):** 1.11 (0.02; 2.60) −0.57 (<−1.78; 4.36) 2.63 (0.30; 6.37)
In the absence of internal dose estimates, when we excluded workers monitored for potential exposure to internal emitters (about 27% of NHL cases), there was no longer any evidence for a linear trend in risk with external dose ($p > 0.5$) and the linear ERR/Sv decreased to 0.19 (95% CI: $-1.55; 2.58$, AIC = 3220.1). There was also no evidence of nonlinearity based on either pure-quadratic model (ERR at 1 Sv = 1.73, 95% CI: $<-3.22; 10.2$, AIC = 3219.6) or the linear-quadratic model ($p = 0.30$). In contrast, retaining internally monitored workers in the analysis but including a two-level factor in the baseline model for whether or not a worker was internally monitored had little effect and the risk estimates were substantially unchanged. The risk estimates for the pure-quadratic model, ERR at 1 Sv was 2.49 (95% CI:$0.23; 6.00$, AIC = 5142.1) and that for the linear model was 1.17 (95% CI: $0.03, 2.76$, AIC = 5142.9).

Further analyses were carried out over various dose range; when the data were restricted to cumulative exposure to below 500 mSv or less than 200 mSv, there was no evidence of a linear trend ($p = 0.40$ and $p = 0.43$ respectively). However, when restricting cumulative doses to less than 100 mSv, there was a significant negative linear trend ($p = 0.04$). The risk estimates decreased as the dose range decreased while the associated CIs widened; for cumulative doses <500 mSv (ERR/Sv = 0.60, 95% CI: $-0.69; 2.33$, N = 701), doses <200 mSv (ERR/Sv = $-0.93$, 95% CI: $-2.82; 1.57$, N = 675) and doses <100 mSv and (ERR/Sv = $-4.26$, 95% CI: $-7.25; -0.32$, N = 642). Fairly similar results were also obtained using the pure-quadratic model (not shown here).

The impact of HWSE in NHL was investigated by adjusting the baseline model to include a two-level factor for duration of employment. There was little impact on the results when either a cut point at 10 years or 30 years was used; both the linear and the pure-quadratic model described the data, but the risk estimates were higher, and the 95% CI were wider using pure-quadratic model. For the linear model with the cut point at 10 years the ERR/Sv was 1.24 (95% CI: $0.05; 2.95$, AIC = 5141.0) and at 30 years it was 1.29 (95% CI: $0.06; 3.03$, AIC = 5142.7). For the pure-quadratic model with the duration of employment factor cut point at 10 years the ERR at 1 Sv was 2.50 (95% CI: $0.23; 6.03$, AIC = 5140.1) and with the cut point at 30 years it was 2.91 (95% CI: $0.32; 7.14$, AIC = 5141.6).

We also investigated if the level of the radiation-related excess risk was modified by a range of factors, such as age and time and the results are presented (table 2). The greatest ERR/Sv for NHL was observed in workers with attained ages of 70 years and older, but a test for differences between attained age groups were not statistically significant ($p > 0.5$). There was also no indication of effect modification by duration of exposure ($p > 0.5$). The risk (ERR/Sv) increased with increasing time since first exposure, but again the differences were not statistically significant ($p > 0.5$). The highest risk was observed for females, industrial workers, those monitored for internal exposure and those with the longest time since last exposure (25 years), but again there was no evidence of statistically significant variation in the ERR/Sv with gender, industrial and non-industrial workers, monitored and unmonitored internal exposure group or time since stop exposure group. The impact of the modifying factors using the pure-quadratic model also investigated and the findings were similar (not shown here). For the main analysis, doses were lagged by 10 years and when alternative lag periods of 5, 15, and 20 years were used, the risk increased with increasing lag periods and the pure-quadratic model still described the data as well as the linear model (table 2).
Table 2. The excess relative risk (ERR/Sv) of NHL and MM incidence in relation to cumulative external exposure by gender, age, age at first exposure and other characteristics of the cohort after adjustment for background factors and lag-periods.

| Person-years           | Non-Hodgkin lymphoma |          | Multiple myeloma |          |
|------------------------|----------------------|----------|------------------|----------|
|                        | No. cases            | ERR/Sv (95% CI) | No. cases | ERR/Sv (95% CI) |
| Gender:                |                      |           |                  |          |
| Male                   | 3 253 535            | 678      | 1.03 (−0.04; 2.50) | 269      | 2.63 (0.29; 6.37) |
| Female                 | 303 299              | 33       | 9.66 (−5.91; 47.5) | 10       | 4.47 (−15.5; 108) |
| p-value                |                      | 0.28     |                  | 0.50     |
| Industrial and non-industrial classification | | | | |
| Industrial             | 1 958 360            | 367      | 1.49 (−0.07; 3.76) | 151      | 3.27 (0.34 8.31)  |
| Non-industrial         | 1 560 761            | 338      | 0.68 (−0.65; 2.55) | 128      | 1.61 (−1.40; 6.96) |
| Unknown                | 37 713               | 6        | 12.0 (−9.5; 65.2)  | 0        | —                    |
| p-value                |                      | 0.45     |                  | 0.50     |
| Attained age           |                      |          |                  |          |
| <50                    | 1 711 190            | 111      | 0.34 (−4.91; 8.66) | 18       | −0.86 (−1.42; >−0.66) |
| 50–<60                 | 896 148              | 169      | −0.02 (−2.17; 3.13) | 54       | 5.60 (<5.14; >7.22) |
| 60–<69                 | 616 120              | 209      | 0.46 (−1.20; 2.81) | 88       | 1.69 (<1.01; >2.67) |
| 70+                    | 333 373              | 222      | 1.89 (0.284; 4.28) | 119      | 1.76 (<1.58; >2.17) |
| p-value                |                      | >0.50    |                  | >0.50    |
| Age at first exposure  |                      |          |                  |          |
| <25                    | 1 550 120            | 159      | 0.35 (−1.09; 2.58) | 40       | 0.81 (<0.25; 1.75) |
| 25–<30                 | 906 166              | 193      | 1.65 (−0.31; 4.50) | 65       | 1.85 (<1.58; 2.09) |
| 30–<40                 | 732 127              | 226      | 1.26 (−0.57; 3.80) | 97       | 2.59 (<2.30; >2.84) |
| 40+                    | 368 414              | 133      | 1.68 (−1.05; 5.74) | 77       | −0.59 (<−4.01; >−0.91) |
| p-value                |                      | >0.50    |                  | >0.50    |
| Time since exposure    |                      |          |                  |          |
| 10–<25                 | 2 150 150            | 220      | 0.18 (−2.74; 4.41) | 65       | 2.88 (<−2.41; >−14.0) |
| 25–<30                 | 558 005              | 118      | 0.90 (−2.20;5.11)  | 53       | 7.81 (<−0.67; 21.4) |
| 30–<40                 | 663 345              | 251      | 1.04 (−0.61; 3.27) | 101      | 0.98 (<−2.07; 5.45) |
| 40+                    | 185 331              | 122      | 1.38 (−0.11; 3.66) | 60       | 3.22 (0.01; 8.93)  |
| p-value                |                      | >0.50    |                  | 0.46     |

(Continued.)
| Person-years | Non-Hodgkin lymphoma | | | Multiple myeloma | | |
|---|---|---|---|---|---|
| | No. cases | ERR/Sv (95% CI) | No. cases | ERR/Sv (95% CI) |
| Duration of exposure | | | | |
| <10 | 2 042 010 | 368 | 0.82 (−4.27; 8.42) | 134 | 0.42 (−12.2; 18.2) |
| 10−<20 | 1 064 020 | 198 | 1.39 (−1.23; 4.89) | 67 | 0.98 (−2.73; 6.77) |
| 20−<30 | 375 889 | 115 | 0.97 (−0.68; 3.15) | 57 | 2.35 (−0.86; 7.36) |
| 30+ | 75 921 | 30 | 1.15 (−0.20; 3.25) | 21 | 3.98 (0.33; 10.4) |
| p-value<sup>c</sup> | >0.50 | >0.50 |
| Monitoring for internal exposure | | | | |
| Yes | 923 766 | 191 | 1.60 (0.23; 3.54) | 87 | 4.35 (0.98; 9.97) |
| No | 2 633 070 | 520 | 0.03 (−1.57; 2.23) | 192 | 0.10 (−2.61; 4.44) |
| p-value<sup>c</sup> | 0.19 | 0.009 |
| Time since left work | | | | |
| <5 | 865 118 | 90 | −0.27 (−2.09; 2.27) | 39 | 7.55 (1.72; 17.9) |
| 5−<15 | 1 268 820 | 195 | 1.75 (0.07; 4.14) | 62 | 0.49 (−2.08; 4.44) |
| 15−<25 | 946 067 | 210 | 1.08 (−0.40; 3.45) | 88 | 2.24 (−1.41; 8.25) |
| 25+ | 476 825 | 216 | 3.17 (−1.87; 10.6) | 90 | 5.15 (−3.30; 20.3) |
| p-value<sup>c</sup> | 0.46 | 0.0165 |
| Other lagging period (years) | | | | |
| 5 | 2.21 (0.16; 5.32)<sup>c</sup> | 1.06 (0.01; 2.485) | 248 (0.25; 6.05) |
| 15 | 2.58 (0.19; 6.30)<sup>c</sup> | 1.14 (−0.01; 2.73) | 2.96 (0.36; 7.09) |
| 20 | 2.93 (0.15; 7.32)<sup>c</sup> | 12.44 (−0.04; 8.02) | 3.30 (0.33; 8.02) |

<sup>a</sup> Background rates adjusted (Model1) and based on 10 year lag period.
<br>
<sup>b</sup> Test of heterogeneity of the ERR/Sv across categories.
<br>
<sup>c</sup> Pure-quadratic fit for NHL (ERR at 1 Sv).
For HL, the trend line and categorical based risk estimates were presented in table 1 and figure 1(b); there was no evidence of an association with radiation dose (ERR/Sv = −0.57, 95% CI: <−1.78; 4.36). The categorical risk estimates show no obvious pattern; the highest estimate was for the cumulative exposure category 0.1–0.2 Sv but it was based on only seven cases. Subsidiary analysis involving the impact for those monitored for internal exposure on external dose did not change the results (not shown here).

3.2. Multiple myeloma
The results of the analysis are also shown in table 1; there was good evidence of a linear association between ionising radiation and MM incidence (p = 0.02). The estimated ERR/Sv was 2.63 (95% CI: 0.30; 6.37, AIC = 2473.2). There was no evidence of nonlinearity in the dose response as AIC value was lower than that AIC value in the linear model based on either the linear-quadratic model (AIC = 2477.6) or pure-quadratic model (AIC = 2476.2). Figure 2 shows reasonably good agreement between a linear trend and fitted RR values for the dose categories. The RR was the highest for the cumulative exposure category above 500 mSv which was about four times larger than that among those with zero dose, but only based on five cases all of whom are workers monitored internal exposure. The impact of the exposures from internal radiation in relation to external dose was examined (to the extent possible without having actual internal dose estimates available); excluding workers monitored for internal exposure resulted in a lack of evidence for a trend in risk with dose (ERR/Sv = 0.38, 95% CI: −2.65; 5.34, p > 0.5). Retaining internally monitored workers in the analysis but incorporating a factor for internal monitoring status into the baseline model led to a decrease in the central estimate of the excess RR (ERR/Sv = 1.80; 95% CI: −0.21; 5.19) and the strength of the evidence for the trend was reduced (p = 0.09), although this estimate was consistent with the result from the main analysis.

A subsidiary analysis was conducted; when the data were restricted to cohort members with external cumulative doses below 500 mSv, 200 mSv and 100 mSv, the evidence for a linear radiation effect weakened (p = 0.066, p = 0.09 and p = 0.05 respectively). The excess RR estimate increased with decreasing dose range and the associated CIs got wider: restricting cumulative doses <500 mSv (ERR/Sv = 2.67 (95% CI: −0.14; 7.05, based on 274 cases)), <200 mSv (ERR/Sv = 4.15 (95% CI: −0.51; 11.0, N = 264)) and <100 mSv (ERR/Sv = 8.01 (95% CI: 0.04; 19.54, N = 251)).

Investigation of the Healthy worker survivor effect revealed that when a factor indicating duration of employment of more than 10 years was implemented in the baseline model, the evidence for a linear dose response relationship was somewhat weakened (p = 0.07) and the ERR/Sv was reduced to 2.07 (95% CI: −0.12; 6.03). Adjusting the baseline model for duration of employment more than 30 years resulted in a further reduction in evidence for an increasing trend in risk with dose (p = 0.18).

There was no evidence that gender, attained age, time since first exposure or age at first exposure factors were significant modifiers of the linear dose response relationship for MM (table 2). The highest risk was observed for industrial workers and also for those workers’ whose time since last exposure was less than 5 years, although there were no significant differences in risk between the industrial/non-industrial groups (p > 0.5) and the was no evidence for variation in risk across the time since last exposure categories (p = 0.165). Risk estimates increased with increasing duration of exposure, but the differences were not
statistically significant ($p > 0.5$). The ERR/Sv was higher in workers monitored for internal exposure compared with unmonitored workers, but there was a lack of evidence that risk varied between these two groups of workers ($p = 0.09$). The further sensitivity of the findings based on the choice of lag period indicated that the ERR/Sv increased with increasing lag period (table 2).

4. Discussion

What makes this study is unique in comparison with previous published NRRW studies examining HL, NHL and MM is that it is the first to use a parametric baseline model and the first to consider the fit of non-linear dose response relationships, and also temporal variation in radiation associated risk to assess the MM and lymphatic cancer risk.

The statistical precision of the estimates in this study was improved for NHL and MM with the longer follow-up by 10 years more in comparison with the previously published NRRW-3 study (Muirhead et al 2009a, 2009b). Number of cases was doubled in comparison with the original third NRRW for NHL from 305 to 711 cases and for MM from 149 to 279 cases. The value of the risk estimates was decreased, the evidence became stronger and the CIs were narrower. For NHL, based on a linear dose response model the ERR/Sv was 1.11 (95% CI: 0.02; 2.60) and a pure-quadratic model also described the dose-response relationship as well as the linear model, but the estimate is double that from the linear model (ERR at 1 Sv = 2.44, 95% CI: 0.22; 5.82). These estimates are consistent with the updated third NRRW analysis of NHL incidence (Haylock et al 2018) and the original third NRRW analysis (Muirhead et al 2009a, 2009b), albeit both using non-parametric baseline modelling. The former study reported a statistically significant increase trend for NHL incidence (ERR/Sv = 1.26, 95% CI: 0.08; 2.94), but a latter one found a weak suggestion based on one-sided test for NHL incidence (ERR/Sv = 1.28, 95% CI: -0.38; 0.46) and no evidence of such a trend from the corresponding mortality analysis was reported (Muirhead et al 2009a, 2009b, Haylock et al 2018).

This current study also showed that the evidence for a positive dose–response relationship disappeared for NHL incidence if the doses were restricted to low doses less than 100 mSv. Also, there was no change for a dose trend after adjusting duration of employment and no evidence for temporal effects in the ERR for NHL was observed. For HL, although the number of cases is doubled in the current study compared to that in the original third NRRW incidence analysis (from 67 to 113 cases), the current incidence data did not show statistically significant associations of HL risk with dose (ERR/Sv = -0.57, 95% CI: <-1.78; 4.36). This estimate is consistent with the previous 3rd NRRW estimate for HL incidence (ERR/Sv = <-1.93, 95% CI: <-1.93; 12.55) and the recent updated NRRW-3 estimate (ERR/Sv = -0.59, 95% CI: <-1.94; 8.92) (Muirhead et al 2009a, 2009b, Haylock et al 2018).

There was good evidence for an increasing linear trend in the risk of MM incidence with external dose (ERR/Sv = 2.63, 95% CI: 0.30; 6.37) but no evidence of nonlinearity in the dose response ($p > 0.5$). The findings from this analysis for MM incidence and the previous analyses are consistent; using non-parametric baseline modelling the updated third NRRW analysis (Haylock et al 2018) showed a significantly increased risk of MM with external dose (ERR/Sv = 2.81, 95% CI: 0.48; 6.96) and a similar pattern to that also reported for MM in the original third analysis of the NRRW (ERR/Sv = 3.60, 95% CI: 0.43; 10.4), although it was accompanied by a caveat that the reliability of the result was low as it was based on few cases with relatively high doses (Muirhead et al 2009a, 2009b). There was no evidence of such a trend from the corresponding mortality analysis; the number of deaths were lower than that incidence analysis, 113 deaths in the original and 175 deaths in the updated third NRRW studies (Muirhead et al 2009a, 2009b, Haylock et al 2018). The strength of the evidence for this study was weakened by restricting data relating to doses under 500 mSv ($p = 0.066$), <200 mSv ($p = 0.09$) and <100 mSv ($p = 0.05$), although their risk estimates were consistent with the overall results.

Duration of employment was considered to be a possible confounder and was therefore included in subsidiary analysis to control for the so-called ‘healthy worker survivor effect’ (Muirhead et al 2009b). This effect can result in negative confounding when workers who are healthier and therefore have lower mortality rates (or cancer incidence rates) stay in employment longer and may accumulate higher doses. When we included adjustment for duration of employment in the analyses, risk estimates actually reduced in magnitude, (ERR/Sv = 2.07), suggesting that a HWSE is unlikely to be an important factor in the analysis of MM risks in this study. The fact that ERR estimates actually decrease on adjustment for duration of employment is likely to be a statistical artefact owing to the fact that length of employment and cumulative dose are highly correlated and therefore the main results are based on a model not using this adjustment.

The NRRW contains good information on external dose, but currently it does not hold information on doses due to internal emitters. In the absence of internal dose estimates, excluding workers who were monitored for internal exposure from the analyses resulted in estimates of trend that were less precise, a substantial proportion of these monitored workers also had relatively high external doses. On the other hand,
the alternative approach of retaining this group but adding a two-level factor of monitoring status to the baseline risk for this group showed similar results to the main analysis for NHL, but not MM. It should be born in mind that even amongst monitored workers in the NRRW cohort their internal doses are likely to be lower than their external doses and indeed some of the monitored workers may not have received any internal dose at all (Muirhead et al 2009a, 2009b). Internal doses from plutonium to lung may sometimes form a substantial proportion of the total occupational dose (Sokolnikov et al 2008, Labutina et al 2013). However, cancers like lymphoma and MM, plutonium deposition leads to relatively little exposure (dose) to these organs (Kuznetsova et al 2016). Consequently, the absent of internal doses is unlikely to have biased our findings for NHL and MM. The Mayak cohort study reported no evidence of a relationship between either external and internal exposures incidence of NHL and MM (Kuznetsova et al 2016).

The observed small number of cases at relatively high doses were amongst those monitored for internal exposure and most of them were BNFL-Sellafield workers who spent their working life over 30 years or more. However, concerned has been raised regarding greater uncertainties associated with individual film badge assessment, especially dosimeters used in the early years of plants at BNFL-Sellafield before 1963 (Kite and Brithcher 1996). As a result, this may be likely that the external doses recorded for these workers at Sellafield could overestimate external doses. Excluding those workers employed at the BNFL-Sellafield site before 1963 (also excludes 43 NHL cases and 13 MM cases), this study showed that the evidence for NHL was not statistically significant anymore (ERR/Sv = 0.75, 95%CI: −0.42; 2.40, p = 0.25) and the evidence for MM was weak (ERR/Sv = 2.44, 95% CI: −0.18; 6.58, p = 0.07). These estimates are all consistent with the unrestricted overall estimates. It is important to note that levels of individual dose were reduced substantially in the 1980s as newer process plant with better shielding against low energy x-rays was introduced (Partington 2000). This early over estimation of external dose for internal workers would certainly be an important effect for those workers with high cumulative doses, noting that recorded external dose rates in the older plutonium process plants were close to the statutory annual limit of 50 mSv. This may provide at least a partial explanation for overestimating external doses amongst plutonium plant workers who are part of the internal radiation workers sub-cohort could lead to attenuation of the dose response, resulting in an underestimation of the risk per unit dose (Gillies and Haylock 2014). In the medium term we expect to be able to acquire internal dose estimates for a significant proportion of the NRRW cohort. These data will then allow the investigation of this issue to be taken further.

Currently underlying mechanisms for these associations are still unclear, although measured and unmeasured confounding factors may have influenced association of external exposure with lymphoma and MM cancer risk. Factors such as immunosuppression or infection were also suggested to be important confounders to altered immune function (Harbron and Pasqual 2020) and certain chemicals (Brown and Rushton 2012). However, in the absence of information on confounding factors, interpretation is difficult.

4.1. Comparison with other studies
Effects of radiation exposure on lymphatic cancers (NHL and HL) and MM have been studied widely among the Japanese A-bomb survivors in the life span study (LSS) cohort, other large group of radiation workers and patients receiving radiotherapy and diagnostic irradiation (Hsu et al 2013, Leuraud et al 2015, Kuznetsova et al 2016). In a review of this literature, analyses of NHL and MM have provided mixed results (UNSCEAR 2008).

Table 3 compares the risk estimates for NHL and MM from the NRRW cohort with those from the LSS cohort and other major radiation workers’ studies. An analysis NHL incidence in the LSS found weak evidence of an elevated risk in men, but no indication of a similar radiation effect in women (Hsu et al 2013). An analysis of deaths from malignant lymphoma (combined NHL and HL) in the LSS (Ozasa et al 2012) similarly found an excess for males, but no association for females and the number of deaths in malignant lymphoma were higher in females (159 deaths) than in males (125 deaths). The NRRW findings are consistent with those results from the Japanese A-bomb data, although the estimates in the NRRW studies are larger than those in the LSS studies. However, this current study found evidence of pure-quadratic model. The differences between this study and those from the LSS study could also be attributed to the magnitude of radiation dose received and the use of dose to whole-body radiation dose equivalent in the NRRW studies, whereas the LSS analyses were based on estimate of dose to bone marrow. In addition, whilst the LSS incidence data point to a strong decrease in ERR/Sv with increasing age or time-since exposure for radiation exposures that arose in childhood, the trend for NHL from this NRRW study is less marked following radiation exposures for males of working age.

Studies of radiation workers other than the NRRW have shown mixed results. A significant association for NHL mortality with radiation exposure was reported in the USA among male radiation workers (ERR/Sv = 8.18; 1.44; 21.2), but the reliability of this result could be questioned as it was based on small number of deaths, 51 deaths (Richardson et al 2009). The international study of nuclear workers INWORKS
### Table 3. Comparison of risk estimates to selected cohort studies.

| Study cohort | Follow-up | Mean dose (Sv) | Non-Hodgkin lymphoma | Hodgkin lymphoma | Multiple myeloma |
|--------------|-----------|----------------|-----------------------|------------------|-----------------|
|              |           |                | No of cases | ERR/Sv (95% CI) | No of cases | ERR/Sv (95% CI) | No of cases | ERR/Sv (95% CI) |
| Updated third NRRW (Current study): 10 year lag period | | | | | | | | |
| Incidence    | 1955–2011 | 0.025          | 711         | 1.11 (0.02; 2.60) | 113          | −0.57 (−1.78; 4.36) | 279          | 2.63 (0.30; 6.37) |
| Mortality    | 1955–2011 | 0.025          | 353         | 1.31 (−0.25; 3.77) | 34           | <−1.93 (−1.93; 26.6) | 175          | 1.50 (−0.42; 5.60) |
| Updated third NRRW (previous): 10 year lag period | | | | | | | | |
| Incidence    | 1955–2001 | 0.025          | 305         | 1.28 (−0.38; 4.06) | 67           | <−1.93 (−1.93; 12.6) | 149          | 3.60 (0.43; 10.4) |
| Mortality    | 1955–2001 | 0.025          | 237         | 0.78 (−0.66; 3.40) | 33           | <−1.93 (−1.93; 32.7) | 113          | 1.19 (−1.08; 7.31) |
| Third NRRW (Original study) | | | | | | | | |
| Incidence    | 1944–2000 | 0.021          | 710         | 0.53 (−0.74; 2.13) | 104          | 2.58 (<NA; 11.0) | 293          | 0.88 (−0.94; 3.45) |
| Mortality    | 1944–2000 | 0.021          | 31          | 0.09 (−1.52; 1.45) | 24           | −0.02 (NA; NA) | 11           | 2.39 (−1.28; 35.5) |
| INWORKS (Combined UK-USA-France studies): 10 year lag period | | | | | | | | |
| Incidence    | 1948–2004 | 0.51           | 31          | 0.46 (−0.08; 1.29) | 35           | 0.20 (−1.03; 2.63) | 136          | 0.38 (−0.23; 7.31) |
| Mortality    | 1950–2003 | 0.51           | 125         | 0.70 (0.08; 1.70) | 93           | 0.54 (−0.04; 1.58) |  | |

*a 90% CI; NA: not available because lower CI bound could not be estimated by AMFIT.

b Pure-quadratic fit at 1 Sv.

c For males.

d Includes NHL and HL.
(Leuraud et al 2015) carried out an analysis of mortality among combined nuclear industry workforces in the US, France and the UK (the nuclear worker subset of NRRW cohort). Unlike the LSS, these workers had exposures similar to the NRRW. However, it did not report an excess risk of NHL. This finding is consistent with our NRRW mortality data, but not for the incidence data. The NRRW estimates are larger than the corresponding INWORKS values, although the CI overlap. The quantitative differences between the results in the NRRW studies and INWORKS can be partly explained by the use of organ dose estimate to red bone marrow in the INWORKS, while the NRRW analyses use whole-body radiation dose equivalent. In addition, there was only a small number of deaths in NHL (five deaths) reported in INWORKS among workers who had accrued doses greater than 0.3 Sv, while the comparable number of cases in the dataset used in these analyses was 26. Analyses of Mayak PA radiation workers in Russia (Kuznetsova et al 2016), based on red bone marrow organ dose and where the external radiation exposure level was much higher than in the NRRW cohort, found no excess of NHL based on 2 year lag period; there were only a few cases (31 cases) and the first case of lymphoma among workers was registered in the Mayak PA mostly within two years after the first employment. The reanalysis of cancer mortality in Canadian nuclear workers reported that NHL was lower compared with the general Canadian population but that was based on only 17 deaths (Zablotska et al 2014). The current study and other NRRW studies found no association between HL incidence and external exposure and this finding is supported by the results based on the mortality and incidence data in other radiation workers’ studies and the LSS, although the risk estimates differed between studies (table 3).

Analyses of MM in other populations exposed to ionising radiation have given mixed results (UNSCEAR 2008). Among the Japanese A-bomb survivors, there was no evidence of statistically significant increases in MM incidence. A higher point estimate was obtained in this study as compared with that derived from the LSS (table 3). Difference in the number of cases (double in the current study), the magnitude of radiation dose received (lower in NRRW cohort), rate of exposure and the use of whole body dose equivalent in NRRW (organ dose to red bone marrow used in the LSS) study may influence the comparability of the dose–response estimates. Some early reports on MM mortality data in the LSS have shown an association with radiation exposure, but there were indications in that study that the mortality findings might have been the result of artefacts due to differential misclassification of myeloma on death certificates (Hsu et al 2013). The authors stated that the A-bomb data provide little, if any, evidence of a radiation effect on MM incidence. INWORKS (Leuraud et al 2015) also reported no evidence of an increasing trend in MM mortality with external dose, although the CIs from the third NRRW studies overlap. This could again be due to small number of deaths at doses above 0.3 Sv (six deaths) in the INWORK study for which organ dose to the red bone marrow dose was used, while in the present study the number of cases was doubled over the same dose range using the whole-body radiation dose equivalent. In this study, when we restricted the data to less than 0.3 Sv, the linear effect was no longer statistically significant ($p = 0.12$, based on 267 cases) with an ERR/Sv of 3.14 (95% CI: −0.61; 8.77). Our central estimate is similar to that from the Mayak workers’ cohort (Kuznetsova et al 2016), but that study found no evidence of radiation risk in MM incidence and number of cases was very low, 11 cases (table 3).

5. Conclusions

Our findings for NHL and MM, in general do not fit well with findings from mortality in other published studies, given that the evidence for an association with radiation in the present study comes primarily from the cancer incidence data. The greater weight would normally be placed on these incidence data than on mortality data because the availability of cancer registration in the UK provide more accurate diagnostic information than mortality data. However, as noted earlier, the results here are dependent on a small number of cases at relatively high doses. Thus, the reliability of this positive result should be treated with caution. Continued follow-up in the NRRW cohort should provide more precise results for these type of cancers as to whether these raised risks are chance findings due to small numbers, particularly at higher doses.

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