Mortality from heart diseases following occupational radiation exposure: analysis of the National Registry for Radiation Workers (NRRW) in the United Kingdom

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Abstract
Statistically significant increases in heart disease (HD) mortality with cumulative recorded occupational radiation dose from external sources were observed among 174,541 subjects, who were predominately exposed to protracted low doses over a number of years, and were followed up until the end of 2011 in the UK National Registry for Radiation Workers (NRRW) cohort. Amongst the subtypes of HD, the increasing trends with cumulative dose arose for ischaemic heart disease (IHD) and other HD (which includes pulmonary HD, valve disorders, cardiomyopathy, cardiac dysrhythmias, carditis, conduction disorder and ill-defined HD). For IHD, the increased mortality appears to be at least 20 years after first exposure and the excess risk peaked between 30 and 40 years after the first exposure. There was no evidence of excess risk of IHD mortality for cumulative radiation doses below 0.1 Sv. A categorical analysis also showed that the risk falls below the expected value based on a linear trend, for cumulative doses greater than 0.4 Sv; this smaller risk appears to be primarily associated with workers who started employment at a younger age and who were employed for longer than 30 years, reflecting possible healthy worker survivor effect. This analysis provided further evidence that low doses of radiation exposure may be associated with increased risk of IHD.

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For other HD, the data suggest an increased risk starting around 40 years after the first exposure. The risk was statistically significant raised only for cumulative doses above 0.4 Sv. However, the number of deaths in this group was small and the results need to be interpreted with caution.

Supplementary material for this article is available online

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Introduction

Radiation-induced heart disease (HD) mortality has been a topic of increased discussion in recent years. The evidence suggests that high dose and high dose rate exposure to ionising radiation increases the risk of HD. Studies of breast cancer patients who were treated with high dose radiation therapy demonstrated evidence of HD mortality several years after radiation exposure (Adams et al 2003, Darby et al 2005, 2013, Schultz-Hector and Trott 2007). At high doses it has been observed that the exposure can cause damage to the structures of the heart and to the coronary artery. The Life Span Study (LSS) of Japanese atomic bomb survivors has also shown evidence of radiation-related excess risk of HD (Shimizu et al 2010, Ozasa et al 2016, 2017, Takahashi et al 2017).

These studies have provided valuable information about radiation risks for HD, but as the exposures received by the LSS participants and medical patients are essentially doses delivered at moderate/high dose rates, they cannot directly address the concerns about the risk of HD from doses accumulated at a low dose rate over many years in an occupational setting and the evidence of potential effects at low doses remains equivocal.

Nuclear worker studies in various countries have been undertaken to directly assess the risks of HD following low dose and low dose rate radiation exposure (Vrijheid et al 2007, McGeoghegan et al 2008, Muirhead et al 2009a, 2009b, Azizova et al 2015). Furthermore, the International Workers Study, INWORKS (Gillies et al 2017), undertook a pooled analysis of mortality from circulatory diseases and other non-cancer outcomes among nuclear workers in France, the United Kingdom and the United States. A statistically significant association between radiation dose and circulatory diseases was observed in this study; within the sub-types of circulatory disease, the study found that ischaemic heart disease (IHD) and stroke mortality are associated with external radiation exposure.

Little et al (2012, 2016) conducted meta-analyses to test the hypothesis of a causal association between low level radiation exposure and circulatory disease. The study included the Japanese atomic-bomb survivors and occupationally exposed groups. It showed a significant association between low doses and low dose rates of ionising radiation and an excess risk of IHD, though it recommended that more detailed epidemiological studies to address potential confounding should be conducted.

Several reviews have presented evidence suggesting an excess radiation induced risk of circulatory disease at occupational and environmental dose levels (McMillan et al 2010, Little et al 2010). In particular, a review by the Health Protection Agency’s Advisory Group on Ionising Radiation (AGIR) (McMillan et al 2010) in the United Kingdom reviewed information on circulatory disease risk based on relevant epidemiological, biological and medical evidence, and it estimated substantial excess risks for IHD, but concluded that an elevated risk was detectable only for exposures above 0.5 Gy. The AGIR report also suggested that many
inflammatory end points potentially relevant to HD may be differentially regulated below and above 0.5 Gy, emphasising the importance of directly assessing risks associated with exposures <0.5 Gy.

To date, the evidence of an effect of radiation exposure on HD risk at low dose levels has been supportive, but heterogeneity observed in the risk between different studies warrants further investigation and there is still very little information on risk modification by age-at-exposure, time-since-exposure or other potentially confounding factors. Continued follow up and analysis of large cohorts are essential to provide more robust evidence of radiation risks at low doses.

The National Registry for Radiation Workers (NRRW) in the UK was set up in 1976 (Goodwin 1975) and provides a unique opportunity to obtain direct information on the risks to health from occupational exposure of chronic low dose rate external radiation. Three main analyses have been performed so far. The latest of these (NRRW-3) found some evidence of a raised risk for circulatory diseases (Muirhead et al 2009a, 2009b). An updated analysis of cancer outcomes in the NRRW-3 cohort with an additional ten years of follow-up has recently been published (Haylock et al 2018). The additional follow-up information has further increased the statistical power and precision of the cancer risk estimates meaning that the NRRW now provides some of the most informative risk estimates available on health outcomes from radiation worker studies.

The aim of this analysis was to examine any potential association between HD and protracted low dose radiation exposure using the same updated NRRW-3 analysis cohort. To maximise statistical power, the analyses first focused on all HD as a single group. However the underlying mechanisms of any radiation effect may differ between subtypes of HD, therefore the risks for IHD and other HD (which includes pulmonary HD, valve disorders, cardiomyopathy, cardiac dysrhythmias, carditis, conduction disorder and ill-defined HD), that arose significantly in relation to radiation dose are examined separately to see if the excess risk varies by time since first exposure or employment length.

Methods

The NRRW cohort consists of workers who were monitored for occupational exposure to external ionising radiation, all of whom were employed by participating organisations, and for whom individual dose records were kept (Muirhead et al 2009b). The data consisted of individual identifiers, date of birth, sex, attained age, employer/facility of employment, industrial status (industrial or non-industrial, i.e. weekly paid or monthly paid, respectively), internal exposure (monitored or not-monitored for intakes of radioactive materials primarily uranium, plutonium and tritium), calendar periods of employment, and external radiation dose histories. The characteristics of the cohort members who contributed to this analysis have been reported previously (Muirhead et al 2009b, Haylock et al 2018). Only about 1% of radiation workers who were eligible have opted out of the cohort.

The external doses received by the workers were measured using personal dosimeters that quantified the penetrating radiation at the surface of the body (Muirhead et al 2009b). The exposures were predominantly from x-rays and gamma rays but with smaller contributions from beta particles and neutrons. The doses were adjusted for the threshold of detection of the workers’ dosimeters (Muirhead et al 1999), while corrections were applied to the historical doses of UKAEA, AWE and BNFL Sellafield workers as were used for the Nuclear Industry Combined Epidemiological Analysis (Carpenter et al 1994), since these personal records of radiation doses were kept primarily to ensure compliance with legal or administrative dose...
limits rather than for the purposes of epidemiological research (Carpenter et al. 1994, Muirhead et al. 1999). The overall mean 10 year lagged lifetime external dose was 23.2 mSv. It was higher amongst the males (25.2 mSv) than the females (5.1 mSv), who only constituted 10% of the cohort. Risk from internal exposure to nuclides such as plutonium, uranium and tritium could not be assessed as there was no quantitative information available regarding internal dose, but only monitoring status.

Mortality follow-up data for this cohort was provided by NHS Digital (formerly the Health and Social Care information Centre) and by National Records of Scotland on an ongoing basis. Compared to the previous NRRW-3 analysis mortality follow-up was extended by ten years to 31 December 2011. By the end of follow-up over 50% of workers who started radiation work before 1960 had died showing the increased maturity of the cohort and improved statistical power (Haylock et al. 2018).

The start of follow-up for each worker was taken to be ten years after the date of start of radiation work with a participating employer, or 10 years following the date on which radiation monitoring data were available, or 1 January 1955, whichever was later; a minimum latent period of ten years is assumed. Follow-up prior to 1955 were excluded, owing to indications of a substantial deficit of deaths relative to national rates meaning deaths in this period might not have been recorded. The end of follow-up for each worker was set to the earliest of their date of death or emigration, their 85th birthday (set to avoid less accurate disease diagnosis at very old ages), or 1 January 2012 (Haylock et al. 2018).

Poisson regression methods for grouped survival data (Breslow and Day 1987) with a stratified baseline hazard function were used to describe the dependence of risk on radiation dose. This type of analysis allowed the efficient estimation of the risk of HD from external radiation having taken into account available non-radiation factors known to modify the baseline risk. In the analyses the person-years and deaths were stratified by non-radiation factors: age (in five-year groups), sex, calendar period (1955—, 1960—, ..., 2010–2011), industrial classification (industrial/non-industrial/unknown) and fifteen first employer groups and were also classified by cumulative external dose in the categories 0—, 10—, 20—, 50—, 100—, 200—, 400+ mSv (Muirhead et al. 2009a, 2009b). Doses were lagged ten years to define the minimum period between exposure and the first possible detection of radiation induced disease. Since the dose distribution was skewed towards low doses, the median dose in each dose category was used for the analysis. All the risk modelling was carried out using the AMFIT module of the Epicure software (Risk Sciences International).

The analyses were based on the underlying cause of death, coded according to the 9th revision of the International Classification of Diseases (ICD9) (WHO 1977). Deaths that were only reported using ICD10 (WHO 1990) were recoded to ICD9 using general equivalence mapping tables (CDC 2016).

While HD was examined as a single group, the data was also analysed by the following subgroups: IHD, rheumatic HD, heart failure, hypertensive HD and other HD.

The primary model used was an excess relative risk (ERR) model of the form:

$$\lambda_{a,c,f,i} = [1 + \text{ERR}(d, e, t, s)],$$

where $\lambda$ represents the background mortality rate, i.e. the rate that would have arisen in the absence of radiation exposure which depends on attained age ($a$), calendar period of employment ($c$), sex ($s$), facility of first employment ($f$) and industrial category ($i$), while the ERR depends on dose-response $\rho(d)$, and can also vary with other parameters such as age-at-exposure, time since exposure and sex. The main dose-response is based on the linear dose-response model $\rho(d) = \beta d$, but nonlinearity in the dose-response was also examined using alternative model such as:
\[ \rho(d) = \gamma d^2, \quad \text{quadratic model} \]
\[ \rho(d) = \beta d + \gamma d^2, \quad \text{linear-quadratic model} \]
\[ \rho(d) = \beta d \exp(\gamma d), \quad \text{linear-exponential model}. \]

Point estimates of the ERR per sievert (ERR/Sv) were estimated by fitting the models and maximising the associated likelihood function. The statistical significance of each model and the 95% confidence intervals (CI) for the ERR were derived using the likelihood ratio statistics.

Results

Table 1 shows the number of deaths subdivided by disease classification (using ICD 9) and ten year lagged cumulative external dose category. In total there were 11,014 HD deaths included in the analysis and of these 9,814 deaths (89%) were attributed to IHD. The other categories of HD include rheumatic HD, heart failure, hypertensive HD, and remainder category of "other HD" (see table 9 for definition); all have relatively small numbers of deaths with the largest grouping of other HD only accounting for 747 (6.8%) of deaths. Disease-specific ERR/Sv estimates are shown in figure 1. The ERR/Sv for all HD as a single group was significantly raised (ERR/Sv = 0.37, 95%CI: 0.11, 0.65; \( p = 0.005 \)). Among the major subgroups of HD, statistically significantly raised risk was found for IHD (ERR/Sv = 0.32; 95%CI 0.04, 0.61; \( p = 0.02 \)) and also for other HD (ERR/Sv = 1.08; 95%CI 0.03, 2.45; \( p = 0.04 \)). The estimated trend for myocardial infarction, which is a major subgroup of IHD, was statistically significant (ERR/Sv = 0.54, 95%CI 0.16, 0.95; \( p = 0.004 \)), while the risk for other IHD was not. There was no evidence that the ERR/Sv differed from zero for heart failure, hypertensive HD and rheumatic HD.

The estimates of ERR/Sv for all HD mortality combined and the subtypes are shown in table 2 along with the ERR for various cumulative external dose categories. These dose-category-specific risk estimates with associated 95% CI for all HD are plotted against the median cumulative dose within each category in figure 2. Also shown in this figure is the linear dose response trend for all HD mortality. Although categorical point estimates can be approximately described by the linear dose response function based on the full dose range, there are notable features among the categorical point estimates for overall HD mortality. For cumulative external dose range <0.1 Sv, the point estimates fluctuates around zero, while in the highest dose category (>0.4 Sv) the estimate is positive but at a level some way below the value expected based on the fitted linear dose response function.

Three alternative dose-response models: the quadratic model, linear–quadratic model and linear–exponential model have also been tested in this analysis. The fitted model parameters are shown in table 3 for overall HD and IHD. The linear dose-response model over the full dose range shows a better fit than the quadratic model for both HD and IHD, based on the difference in deviance values. There are no statistically significant differences between linear and linear–quadratic dose-response model (\( p = 0.238 \)), and no difference between linear and linear–exponential model (\( p = 0.324 \)) for overall HD mortality. In the case of IHD mortality risk, the linear–quadratic model shows a better fit than the linear model and the difference between these models is statistically significant (\( p = 0.048 \)). However, when the dose range is restricted to less than 0.4 Sv, the nonlinearity in the dose-response relationship disappears and the difference between these models loses its statistical significance.

Figure 3 shows the ERR/Sv for all HD mortality derived using the full cumulative external dose range and the dose range excluding person-year experience exceeding 0.4, 0.2,
Table 1. Disease category and observed deaths by dose category (mSv) with ten years lagged dose.

| Cause of death                  | ICD 9 code          | <10 | 10–20 | 20–50 | 50–100 | 100–200 | 200–400 | 400+ | Total number of deaths |
|---------------------------------|---------------------|-----|-------|-------|--------|---------|---------|------|-----------------------|
| **Heart diseases**              |                     |     |       |       |        |         |         |      |                       |
| Ischaemic heart disease (IHD)   | 393–398, 402, 404, 410–429 | 5658| 1351  | 1647  | 977    | 683     | 455     | 243  | 11,014                |
| Myocardial infarction           | 410–414             | 4991| 1214  | 1465  | 892    | 628     | 413     | 211  | 9,814                 |
| Other IHD                       | 411–414             | 2030| 458   | 559   | 324    | 218     | 153     | 81   | 3,823                 |
| Rheumatic HD                    | 393–398             | 36  | 10    | 7     | 3      | 5       | 2       | 1    | 64                    |
| Heart failure                   | 428                 | 129 | 30    | 40    | 23     | 8       | 13      | 6    | 249                   |
| Hypertensive HD                 | 402, 404            | 81  | 23    | 15    | 11     | 5       | 3       | 2    | 140                   |
| Other heart diseases            | 415–427, 429        | 421 | 74    | 120   | 48     | 37      | 24      | 23   | 747                   |
0.1 and 0.05 Sv, respectively. The ERR/Sv point estimate increases when the dose range is restricted to doses less than 0.4 Sv, which is consistent with the observations in figure 2 showing that the ERR decreases above 0.4 Sv. When the dose range is restricted to <0.2 Sv, the ERR/Sv started to decrease and there is no evidence for radiation risk for HD mortality when the dose range restricted to cumulative doses below 0.1 Sv. At the dose range below 0.05 Sv, the ERR/Sv becomes negative but it is not statistically significant. The risk estimates for different cumulative external dose ranges are listed in table 4 for all HD and its subtypes.

Table 5 summarises the results of fitting the linear dose response relationship to all HD, IHD and other HD respectively, and allowing the slope of the dose response to vary by the
Table 2. Observed ERR/Sv for heart disease mortality and its subtype, along with ERR by cumulative external dose category (mSv) based on with ten years lagged dose.

| Cause of death       | Total deaths | ERR/Sv (95% CI) | p-value | 10-20 | 20-50 | 50-100 | 100-200 | 200-400 | 400+ |
|----------------------|--------------|-----------------|---------|-------|-------|--------|---------|---------|------|
| Heart diseases       | 11 014       | 0.37 (0.11, 0.65) | 0.005   | 0.01 (−0.05, 0.08) | −0.04 (−0.09, 0.02) | 0.02 (−0.05, 0.09) | 0.06 (−0.03, 0.16) | 0.18 (0.06, 0.31) | 0.10 (−0.04, 0.27) |
| IHD                  | 9814         | 0.32 (0.04, 0.61) | 0.022   | 0.03 (−0.04, 0.10) | −0.04 (−0.10, 0.02) | 0.04 (−0.04, 0.12) | 0.09 (−0.01, 0.19) | 0.18 (0.06, 0.32) | 0.06 (−0.09, 0.22) |
| Myocardial infarction| 5991         | 0.54 (0.16, 0.95) | 0.004   | 0.04 (−0.04, 0.13) | −0.03 (−0.11, 0.05) | 0.08 (−0.02, 0.19) | 0.17 (0.04, 0.31) | 0.22 (0.06, 0.40) | 0.15 (−0.06, 0.38) |
| Other IHD            | 3823         | 0.01 (−0.36, 0.45) | >0.5    | 0.01 (−0.09, 0.13) | −0.05 (−0.14, 0.05) | −0.03 (−0.14, 0.10) | −0.03 (−0.17, 0.12) | 0.12 (−0.07, 0.34) | −0.08 (−0.27, 0.18) |
| Rheumatic HD         | 64           | −0.59 (−1.89, 4.60) | >0.5    | −0.07 (−0.57, 0.86) | −0.44 (−0.78, 0.23) | −0.58 (−0.90, 0.25) | 0.07 (−0.65, 1.75) | −0.36 (−0.93, 1.77) | −0.34 (−0.98, 3.28) |
| Heart failure        | 249          | 0.72 (−0.77, 3.21) | 0.410   | −0.09 (−0.41, 0.35) | −0.03 (−0.34, 0.41) | 0.03 (−0.37, 0.62) | −0.44 (−0.75, 0.11) | 0.60 (−0.18, 1.93) | 0.28 (−0.53, 1.90) |
| Hypertensive HD      | 140          | 0.06 (−1.57, 4.00) | >0.5    | 0.29 (−0.22, 1.06) | −0.26 (−0.60, 0.27) | 0.14 (−0.44, 1.15) | −0.14 (−0.71, 1.03) | −0.08 (−0.79, 1.73) | 0.25 (−0.87, 4.50) |
| Other heart diseases | 747          | 1.08 (0.03, 2.45) | 0.040   | −0.21 (−0.39, 0.01) | 0.03 (−0.17, 0.28) | −0.23 (−0.44, 0.04) | −0.08 (−0.37, 0.30) | 0.08 (−0.33, 0.65) | 0.86 (0.13, 1.93) |
categorical variables: sex, whether the worker was monitored for internal exposure, industrial status, age-at-first-exposure, time since first exposure, attained age and employment length. In this study, female workers generally had smaller exposures than males and only account for 256 HD deaths compared to 10,758 HD deaths for males. Therefore, the female specific analysis lacked the statistical power needed to be informative, and overall radiation risk estimate is dominated by male workers. The ERR/Sv point estimate for workers not monitored for internal exposure was somewhat higher than that of monitored workers, particularly for IHD where the excess risk doubled for non-monitored workers in comparison with monitored workers. However, a heterogeneity test showed that the difference was not statistically significant. There was no evidence of difference in risk with respect to industrial status ($p > 0.5$).

To further investigate possible confounding by socioeconomic status among monitored and non-monitored workers, the mortality experience of these groups was examined separately according to the radiation exposure and industrial status which crudely reflects the socioeconomic status. Table 6 shows the number of deaths and ERRs due to radiation exposure in four separate subgroups for HD, IHD and other HD. There was no statistically significant difference detected in ERR/Sv among these subgroups. This suggests that the socioeconomic status is not a major confounding factor in our analysis, and the difference in ERR/Sv is not statistically significant between the workers who were monitored for internal exposure and those who were not.

The effect of age-at-first-exposure on the dose response relationship was examined by considering variation in risk across three age at first exposure groups, $<30$, $30–45$, and $45+$ years old (table 5). There was no evidence of variation in the ERR/Sv estimates across the categories ($p > 0.5$). Also illustrated in figure 4 are the results of the analysis of the variation in ERR/Sv with time since first radiation exposure. There is no evidence of increased risk during the first 20 years after first radiation exposure, but thereafter the excess risk point estimate rose to a peak value for the 30–40 year group before declining again. However a test of heterogeneity between the groups was not statistically significant.
Table 3. Model parameters of linear, quadratic, linear–quadratic, linear–exponential models for heart disease and IHD.

| Model          | Heart disease (full dose range) | IHD (full dose range) | IHD (Median dose <0.4 Sv) |
|----------------|---------------------------------|-----------------------|---------------------------|
|                | ERR /Sv (95%CI)                 | ERR/Sv (95%CI)        | ERR/Sv (95%CI)            |
|                | β  | γ  | Dev. | p-value | β  | γ  | Dev. | p-value | β  | γ  | Dev. | p-value |
| Linear         | 0.37 (0.11, 0.65)               | 0.32 (0.04, 0.61)     | 0.70 (0.27, 1.16)         | 38 160 | 35 445 |
| Quadratic      | 0.59 (0.04, 1.20)               | 0.38 (−0.18, 1.00)    | 1.68 (1.14, 4.77)         | 38 164 | 35 448 |
| Linear–quadratic | 0.73 (0.08, 1.42)               | 0.96 (0.26, 1.70)     | 0.32 (−0.78, 1.48)        | 38 159 | 35 441 |
| Linear–exponential | 0.67 (0.09, 1.59)               | 0.95 (0.16, 2.10)     | 0.43 (−0.44, 1.57)        | 38 159 | 35 442 |
|                | −0.86 (−2.33, 0.56)             | −1.52 (−3.06, −0.01)  | 2.18 (−3.824, >44)        | 0.238 | 0.048 |
|                | −1.45 (−4.50, 2.16)             | −2.57 (−6.2, 0.70)    | 34 201 >0.5              | 0.324 | 0.099 |

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Some workers terminated their employment in the nuclear industry many years before their normal retirement age. We have examined the effects on the radiation-associated risk due to earlier termination of employment from the nuclear industry. Table 7 shows the ERR/Sv according to the number of years prior to normal retirement age the workers ceased employment. The retirement age varied over time, from 60 years early in the study to 65 years in recent years. To simplify the presentation of results, we used 60 years of age as the retirement age. The workers who were employed beyond 60 years of age were categorised into the <3 years group from retirement so that they were also included in the analysis, as shown in table 7. For the all HD and IHD, it appears that there is no radiation risk for those workers who stopped radiation work more than 15 years before their retirement age, but statistically significant raised risks were found for workers who left the nuclear industry between six and 14 years before retirement age. The radiation risk starts to decrease again for those workers who stayed in employment until close to (within five years of) retirement age and beyond. The same analysis was performed for the different age-at-first-exposure subgroups, and the results are shown in table 8. For the older age group 45+ years, only those workers who stayed in employment until close to retirement age showed an increased radiation associated risk, whereas workers who terminated their employment more than three years before retirement showed a negative ERR/Sv for HD and IHD although in both cases the risk was not statistically significant. For the 30–45 years age-at-first-exposure group, negative risk estimates were obtained for workers who terminated their employment 15 or more years before retirement age, although estimates were not statistically significant. The radiation associated risk became positive for workers who left employment between six and 14 years before the retirement age, but decreased again for those stayed in the employment until the retirement. For the youngest age-at-first-exposure group, the radiation-associated risk estimates were raised across all the categories of employment ending period. For workers who left employment 15 or more years before retirement age, the risk estimate was 0.64 (−0.51, 2.03); but increased to 2.58 (0.41, 5.42) for workers who terminated their employment six to nine years before the retirement age, but among those workers who remained in employment until close to retirement the risk decreased to 0.43 (−0.07, 1.04).
Table 4. ERR/Sv over different cumulative external dose ranges for heart disease mortality and its subtypes.

| Diseases              | ERR/Sv (95% CI) estimates when excluding person-year experience above a specified dose level |
|-----------------------|------------------------------------------------------------------------------------------------|
|                       | All dose | <0.4 Sv | <0.20 Sv | <0.1 Sv | <0.05 Sv |
| Heart                 |          |         |          |         |          |
| IHD                   | 0.37 (0.11, 0.65) | 0.64 (0.24, 1.06) | 0.44 (−0.18, 1.09) | −0.08 (−1.09, 0.99) | −1.50 (−3.34, 0.44) |
| Myocardial infarction | 0.54 (0.16, 0.95) | 1.00 (0.43, 1.63) | 1.31 (0.42, 2.28) | 0.77 (−0.64, 2.30) | −1.05 (−3.56, 1.65) |
| Other IHD             | 0.01 (−0.36, 0.45) | 0.26 (−0.35, 0.95) | −0.36 (−1.30, 0.69) | −0.70 (−2.33, 1.09) | −1.94 (−4.98, 1.39) |
| Rheumatic HD          | −0.59 (−1.89, 4.60) | −0.90 (−3.26, 5.10) | −1.05 (−5.31, 8.25) | −8.40 (−13.22, 3.55) | −12.86 (−24.94, 12.00) |
| Heart failure         | 0.72 (−0.77, 3.21) | 0.81 (−1.34, 4.20) | −2.50 (−5.14, 1.73) | −0.25 (−5.79, 7.78) | −1.95 (−12.04, 12.37) |
| Hypertensive HD       | 0.06 (−1.57, 4.00) | −0.36 (−2.88, 4.88) | −0.23 (−4.70, 7.73) | 0.47 (−7.17, 13.23) | −5.85 (−18.33, 14.59) |
| Other heart diseases  | 1.07 (0.03, 2.49) | −0.003 (−1.31, 1.73) | −0.99 (−2.93, 1.50) | −2.93 (−6.12, 1.09) | −0.82 (−7.29, 7.09) |
Table 5. ERR/Sv of overall heart disease mortality, ischaemic heart disease mortality and other heart disease mortality, varies by sex, internal monitored status, industrial status, age-at-first-exposure, time-since-first-exposure, attained age, and length of employment. 112 subjects with unknown industrial status were excluded from the analysis.

|                         | Number of death for all heart diseases | All heart diseases | Subtype: ischaemic HD | Subtype: other heart diseases |
|-------------------------|----------------------------------------|-------------------|----------------------|-----------------------------|
| **Sex**                 |                                        |                   |                      |                             |
| Male                    | 10 758                                 | 0.36 (0.06, 0.69) | 0.32 (0.01, 0.66)    | 0.67 (−0.01, 1.45)          |
| Female                  | 256                                    | 1.27 (−1.7, 8.2)  | −0.19 (−1.88, 6.24)  | −1.94 (NC, NC)              |
| **p-value for the Heterogeneity test** |                                        |                   |                      |                             |
| Monitored for internal  |                                        |                   |                      |                             |
| Yes                     | 3615                                   | 0.32 (0.04, 0.63) | 0.25 (−0.03, 0.57)   | 1.01 (−0.09, 2.52)          |
| No                      | 7399                                   | 0.54 (0.05, 1.09) | 0.54 (0.03, 1.12)    | −1.94 (NC, NC)              |
| **Industrial status**   |                                        |                   |                      |                             |
| Industrial              | 7234                                   | 0.35 (0.03, 0.69) | 0.28 (−0.04, 0.64)   | 1.06 (−0.19, 2.87)          |
| Non-industrial          | 3668                                   | 0.38 (−0.08, 0.90) | 0.37 (−0.11, 0.93)  | 1.14 (−0.49, 3.82)          |
| **p-value for the Heterogeneity test** |                                        |                   |                      |                             |
| **Age-at-first exposure** |                                        |                   |                      |                             |
| <30                     | 2727                                   | 0.26 (−0.12, 0.68) | 0.11 (−0.27, 0.54)  | 1.92 (0.16, 4.48)           |
| 30–45                   | 4832                                   | 0.47 (0.13, 0.85) | 0.45 (0.09, 0.85)    | 1.02 (−0.27, 2.89)          |
| 45+                     | 3455                                   | 0.26 (−0.35, 0.97) | 0.40 (−0.27, 1.18)  | −0.82 (−1.90, 2.44)         |
| **p-value for the Heterogeneity test** |                                        |                   |                      |                             |
| **Time since first exposure** |                                        |                   |                      |                             |
| 10–20                   | 2583                                   | −0.08 (−0.96, 1.00) | 0.04 (−0.90, 1.20)  | 0.16 (NC, 7.82)             |
| 20–30                   | 3377                                   | 0.15 (−0.29, 0.65) | 0.24 (−0.24, 0.78)  | 0.10 (−1.34, 2.67)          |
| 30–40                   | 3026                                   | 0.55 (0.14, 1.01) | 0.54 (0.11, 1.02)    | 0.18 (−1.05, 2.19)          |
| 40–50                   | 1623                                   | 0.51 (0.05, 1.02) | 0.33 (−0.13, 0.85)  | 2.77 (0.60, 5.98)           |
| 50+                     | 405                                    | 0.10 (−0.53, 0.88) | −0.17 (−0.78, 0.63) | 1.67 (−0.57, 5.74)          |
| **p-value for the Heterogeneity test** |                                        |                   |                      |                             |
### Table 5. (Continued.)

| Attained age | ERR/Sv (95%CI) |
|--------------|---------------|
|              | All heart diseases | Subtype: ischaemic HD | Subtype: other heart diseases |
| <50          | 606            | 0.93 (−0.65, 3.25)   | 1.44 (−0.37, 4.08)          | −1.94 (NC, 10.49) |
| 50–60        | 1772           | 0.94 (0.06, 2.01)    | 0.94 (0.02, 2.07)           | 1.96 (−1.18, 9.36) |
| 60–70        | 3378           | 0.02 (−0.41, 0.51)   | −0.09 (−0.52, 0.40)         | 2.44 (−0.24, 7.33) |
| 70–80        | 3931           | 0.43 (0.05, 0.87)    | 0.40 (−0.01, 0.87)          | 0.48 (−0.63, 2.19) |
| 80+          | 1327           | 0.42 (0.04, 0.87)    | 0.36 (−0.34, 1.26)          | 1.84 (−0.65, 6.77) |

**p-value for the heterogeneity test**  
Employment length  
<10          | 5483           | 0.90 (−0.06, 1.98)   | 0.73 (−0.28, 1.88)          | 1.87 (−1.52, 7.97) |
| 10–20       | 2820           | 0.58 (0.05, 1.17)    | 0.70 (0.13, 1.35)           | −0.35 (−1.81, 2.59) |
| 20–30       | 1914           | 0.54 (0.16, 0.97)    | 0.57 (0.16, 1.02)           | −0.13 (−1.26, 1.67) |
| >30         | 797            | 0.11 (−0.23, 0.49)   | −0.07 (−0.40, 0.32)         | 2.68 (0.83, 5.32)  |

**p-value for the heterogeneity test**  
Alternative lagging strategies Lag time (years)  
10          | 11 014         | 0.37 (0.11, 0.65)    | 0.32 (0.04, 0.61)           | 1.08 (0.03, 2.49)  |
| 15          | 11 014         | 0.49 (0.20, 0.81)    | 0.40 (0.10, 0.74)           | 1.42 (0.24, 3.01)  |
| 20          | 11 014         | 0.51 (0.18, 0.88)    | 0.38 (0.04, 0.75)           | 1.83 (0.44, 3.73)  |
Table 6. Excess relative risks for the four categories of employment and radiation exposure status.

| Cause of death | Number of deaths, ERR/Sv (95%CI) | p-value for heterogeneity test |
|----------------|----------------------------------|-----------------------------|
|                | Monitored for internal exposure | Non-monitored for internal exposure |
|                |                                 |                             |
|                |                                 |                             | >0.5 |
| Heart disease  | 2537, 0.31 (−0.02, 0.68)         | 4697, 0.47 (−0.12, 1.13)    | >0.5 |
| IHD            | 2275, 0.20 (−0.14, 0.58)         | 4194, 0.57 (−0.05, 1.27)    | >0.5 |
| Other HD       | 148, 1.25 (−0.13, 3.32)          | 300, 0.19 (<−2.17, 3.62)    | >0.5 |
|                | 1074, 0.32 (−0.17, 0.88)         | 2594, 0.60 (−0.25, 1.63)    | >0.5 |
|                | 967, 0.36 (−0.15, 0.96)          | 2281, 0.42 (−0.44, 1.49)    | >0.5 |
|                | 81, 0.59 (−0.90, 3.22)           | 208, 3.26 (−0.32, 9.09)     | >0.5 |
The dose response relationship for IHD is very similar to that of overall HD mortality as the number of deaths in the IHD group makes up 89% of the total deaths from HD. The ERR estimates by dose category rise to a peak for the 0.20–0.4 Sv category, before dropping at doses above 0.4 Sv (figure S1 is available online at stacks.iop.org/JRP/39/327/mmedia).

The dose response relationship for the group of other HD has a different pattern of variation by dose category from that for IHD. There was no clear increase in ERR below 0.4 Sv, but a statistically significant increase was observed for the highest dose category >0.4 Sv (figure S2). This may be an indication that the risk of radiation induced mortality for the group of other HD occurs only at a much higher dose level than that for IHD for which the ERR started to increase at a dose level above 0.1 Sv. A more detailed breakdown of diseases within the category of other HD is listed in table 9. Raised risks are observed for most of the subtypes of other HD, in particular a statistically significantly raised risk was observed for cardiac dysrhythmias based on 92 deaths.

The ERR/Sv for IHD and other HD for the full cumulative external dose ranges, and dose range excluding person-year experience exceeding 0.4, 0.20, 0.1 and 0.05 Sv are shown in figures S3 and S4 respectively. For IHD, there was no statistically significant increase in risk for doses below 0.1 Sv. The risk estimate was negative for doses below 0.05 Sv though not significantly so. For the other HD group, there was no excess risk from radiation exposure at doses below 0.4 Sv.

Variation in ERR/Sv with time-since-first-exposure categories are shown for IHD and other HD mortality in figures S5 and S6. For IHD the ERR/Sv point estimate peaked 30–40 years after first radiation exposure and remained positive up to 50 years after first exposure. For the group of other HD, a statistically significant raised risk was only observed 40–50 years after first exposure and declined thereafter. Although no indication of strong effect modification by attained age, the ERR point estimate appears to decrease with increasing attained age for all HD and IHD (table 5).

Variation of ERR/Sv estimates by length of employment for HD, IHD and other HD mortality are shown in table 5 (also illustrated in figures 5, S7 and S8).
Table 7. Excess relative risks for heart disease, IHD and other heart diseases by employment status.

| Termination years before retirement age of 60 (years) | Heart diseases | IHD | Other heart dis. |
|------------------------------------------------------|----------------|-----|------------------|
|                                                       | Deaths | ERR/Sv (95%CI) | Deaths | ERR/Sv (95%CI) | Deaths | ERR/Sv (95%CI) |
| <3<sup>a</sup>                                         | 5258   | 0.31 (0.05, 0.60) | 4694   | 0.26 (−0.01, 0.57) | 334    | 1.10 (0.01, 2.59) |
| 3–5                                                  | 783    | 0.13 (−0.83, 1.31) | 697    | 0.07 (−0.93, 1.32) | 58     | −0.19 (<−4.66, 7.06) |
| 6–9                                                  | 899    | 1.59 (0.23, 3.22) | 809    | 1.63 (0.22, 3.33) | 50     | 1.76 (<−3.54, 10.18) |
| 10–14                                                | 774    | 2.03 (0.58, 3.75) | 678    | 1.81 (0.33, 3.59) | 55     | −1.16 (<−5.23, 5.81) |
| 15+                                                  | 3300   | −0.04 (−0.84, 0.90) | 2936   | −0.21 (−1.04, 0.77) | 250    | 2.06 (−1.10, 7.32) |
| p-value for heterogeneity test                        | 0.046  |                   | 0.060  |                   | >0.5   |                   |

<sup>a</sup> Workers employed beyond age 60 are also included in this group.
Table 8. Excess relative risks for heart disease, IHD and other heart diseases by employment status for the different age-at-first-exposure groups.

| Termination years before retirement age of 60 (years) | Heart diseases | IHD | Heart diseases | IHD | Heart diseases | IHD |
|------------------------------------------------------|----------------|-----|----------------|-----|----------------|-----|
| <3a                                                  | 541 (−0.07, 1.04) | 478 (−0.17, 1.01) | 2101 (−0.02, 0.76) | 1901 (−0.15, 0.65) | 2616 (−0.44, 0.96) | 2315 (−0.31, 1.27) |
| 3–5                                                  | 127 (−0.61, 2.67) | 112 (−0.81, 2.60) | 292 (−1.96, 1.77) | 264 (−1.85, 1.96) | 364 (−4.33, 2.27) | 321 (−4.32, 2.66) |
| 6–9                                                  | 137 (0.41, 5.42)  | 120 (0.09, 5.13)  | 376 (−0.44, 3.90) | 347 (−0.10, 4.77) | 386 (−4.13, 2.89) | 342 (−4.65, 2.95) |
| 10–14                                                | 172 (0.20, 5.49)  | 148 (0.18, 5.76)  | 513 (0.37, 4.87)  | 460 (−0.14, 4.32) | 89 (−2.65, −9.72) | 70 (−3.43, −3.65) |
| 15+                                                  | 1750 (−0.51, 2.03) | 1541 (−0.56, 2.14) | 1550 (−1.98, 0.64) | 1395 (−2.32, 0.11) | 0 | 0 |
| p-value                                              | 0.024           | 0.266         | 0.07             | 0.0398          | 0.412        | 0.336         |

a Workers employed beyond age 60 are also included in this group.
ERR/Sv estimates were raised for workers employed for less than 30 years, but only for the categories 10–20, 20–30 years were the estimates significantly raised. The excess risk for IHD is almost zero for the workers employed for over 30 years, i.e. workers employed at a younger age, <30 years old, when they first started radiation work. For other HD the reverse pattern was observed with a significantly raised ERR/Sv only seen for workers employed longer than 30 years.

The main analysis in this paper was based on ten year lagged doses. However, results for other alternative lagging periods 15 and 20 years were also tested. The results are shown in table 5. Radiation-associated risks are increased somewhat using longer dose lagging methods.

**Discussion**

In this analysis, a statistically significant increase in HD mortality among 174,541 subjects was observed in relation to cumulative occupational radiation exposure from external sources.
Increased risk of HD mortality appeared 20 years after first exposure, and was mainly driven by increased risk of IHD mortality. There was no evidence of excess risk of HD mortality at cumulative radiation dose below 0.1 Sv, and the ERR was smaller than the expected value based on a linear trend for cumulative doses greater than 0.4 Sv. A comparison of overall results from this analysis with those from other studies was made and the specific features observed in our analysis are discussed in the following subsections.

**Comparison with other studies**

The overall HD mortality results agree with those from the LSS cohort (Ozasa et al. 2017, Takahashi et al. 2017) where significant positive associations were observed with radiation dose. However, subtype-specific analysis showed different results between our analysis and the LSS study. In our analysis, increased risk was observed from IHD, but there was no evidence of raised risk of rheumatic or hypertensive HD. Although a raised risk was observed for heart failure, it was not statistically significant. The LSS showed a significant increases in risk with dose for vavular diseases, rheumatic HD, hypertensive organ damage and heart failure. There was also no evidence in the LSS of increases in risk with dose for IHD and its subtype of myocardial infarction. The differences between the two studies are of interest and could be partly attributed to the different background disease rates of the populations. For example, Western populations tend to have a much higher fat diet than the Japanese population which results in higher rates of IHD in the NRRW cohort (Levy 2013). In the presence of elevated cholesterol levels, radiation exposure might accelerate atherogenesis (McMillan et al. 2010). In Japan, the most dominant HD risk is from hypertension (Ozasa et al. 2016); the rates of IHD (Iso 2011) are much lower than the western population. The low rates of IHD coupled with possible misclassification of the disease with heart failure could also result in a low statistical power for detecting any radiation-associated risk for IHD and make comparison between studies difficult.

There have been studies concerning occupational low dose and low dose rate radiation exposures, for example, a statistically significant association between cumulative radiation dose from photon radiation and circulatory disease mortality was observed in INWORKS (Gillies et al. 2017), an important component of which is the NRRW. Within the sub-types of circulatory disease, an association between mortality and cumulative dose was observed for IHD (ERR/Sv = 0.17, 90%CI: 0.002, 0.36). Similar risk estimates were also found among the Russian Federation Mayak nuclear workers (Azizova et al. 2015) : a significant increasing linear trend in IHD incidence with increasing external dose was found after adjusting for non-radiation factors and internal plutonium dose (ERR/Gy = 0.10, 95%CI: 0.04, 0.17). An assessment was performed on radiation-associated risks of mortality from circulatory disease in the cohorts of Mayak and Sellafield nuclear workers (Azizova et al. 2018). The ERR/Sv estimates in relation to external exposure were significantly raised in both cohorts for IHD, but also differed significantly between the two cohorts. By examining the ERR/Sv for the two periods of first employment of the Mayak and Sellafield cohorts, it was found that the heterogeneity in ERR/Sv was confined to the earlier sub-cohorts and the ERR/Sv for the later subcohorts were compatible. The pooled analysis of the two subcohorts for the later first employment period produced an ERR/Sv of 0.22 (95%CI: −0.06, 0.57). Furthermore, radiation associated circulatory disease mortality at dose level <0.5 Gy has been reported in a pooled analysis of 77,275 patients from the Massachusetts and Canadian tuberculosis fluoroscopy cohorts (Tran et al. 2017). It found that there was statistically significant increasing trends with cumulative dose for IHD mortality (ERR/Gy = 0.267; 95%CI: 0.003, 0.552). However, in this study, the doses had to be reconstructed, confounding factors such as
lifestyle and medical risk factors for circulatory disease could not be entirely excluded. All of these factors might have a significant impact on the risk estimates. Nevertheless, the risk estimates from the aforementioned studies are of the same order of magnitude to our finding for IHD (ERR/Sv = 0.32, 95%CI: 0.04, 0.61).

**Risk at very low dose <0.05 Sv**

We examined how the ERR/Sv changed over different cumulative dose ranges by progressively excluding doses above 0.4, 0.2, 0.1 and 0.05 Sv. The risk estimates for the different dose ranges revealed that the radiation-associated risk decreases as the upper limit of the dose range decreases starting at 0.4 Sv. Although they were not statistically significant, the risk estimates for overall HD mortality and its subtypes appeared to be below zero at cumulative doses <0.05 Sv (figures 3, S3 and S4). Whether this could indicate some kind of beneficial effect on HD risk at very low dose is unclear and requires further investigation with longer follow-up. Similar results for IHD have also been observed in INWORKS (Gillies et al 2017), but no firm conclusion can be drawn because the finding was not statistically significant. Table 8 presents the ERR/Sv by employment status for HD and IHD. The results indicated that for workers employed for a relatively short time period and who therefore received a relatively low cumulative dose, the ERR/Sv tends to be small or even negative. This is the case especially for the older age-at-first-exposure group 45+ years, although these risk estimates are not statistically significant in these subgroup analyses. It is worth bearing in mind in relation to this result that some experimental studies have found that exposure to low doses below 0.5 Gy may potentially have anti-inflammatory effects (Roedel et al 2002, 2007, Mitchel et al 2011, Stewart et al 2013). This could possibly slow the progression of HD. In this analysis, the ERR/Sv for overall HD mortality was near zero at cumulative doses <0.1 Sv as shown in figure 3. These observations could be taken as support for possibility that inflammatory effects relevant to HD may be differentially regulated around 0.1 Gy; clearly further experimental work is required before a firm conclusion can be drawn.

**Time from initial exposure to first increase in HD risk**

As illustrated in figure 4, no raised radiation-associated risk for HD mortality with cumulative dose was observed until about 20 years after the first radiation exposure. Subsequently, the point estimate of ERR/Sv started to increase over the following ten years, and peaked between 30 and 40 years after first exposure. After 50 years, the ERR/Sv started to diminish. A similar pattern was observed for IHD risk (figure S5) which is not surprising given that IHD is by far the most common form of HD. A person who started employment between 18 and 30 years of age, and who survives at least 50 years, would be in the age range 68–80 years, when the underlying risk of HD is known to be high. The low ERR/Sv of IHD more than 50 years after first exposure indicates that radiation-associated risk is low for some of the young workers, i.e. those less than 30 years old when they are first exposed. However, the excess number of deaths associated with radiation exposure is the product of ERR and baseline rate, which may not reduce substantially because of high baseline rate for HD at old ages.

For the group of other HD, the statistically significant raised ERR/Sv only appeared 40 years after first exposure and the raised radiation-associated risk remained for 50+ years after first exposure (figure S6). This result is dependent on the group of workers who began radiation work before <30 years of age. Analysis of length of employment revealed that raised ERR/Sv for IHD mortality was mainly seen among workers who were employed for
less than 30 years. In contrast, there was a statistically significant raised radiation-associated risk of other HD among workers employed more than 30 years. The workers who are most likely to work for longer than 30 years are those who started radiation work at young age, i.e. less than 30 years old. This indicates that some of the younger workers had a smaller radiation-associated risk for IHD if they were in employment for over 30 years, but ERR/Sv for other HD rose after 30 years of employment. However, the number of deaths in the other HD group was much smaller than that of the IHD group, so its impact on the overall HD risk was limited.

Risk at cumulative doses >0.4 Sv

In the dose-response relationship for HD mortality and IHD mortality (shown in figures 2 and S1), there were distinct features for the ERR/Sv estimates at cumulative doses above 0.4 Sv. The risk estimates at this dose level dropped below the linear trend formed by using all data. This drop in risk estimate has an effect on the shape of dose response. Apart from the linear dose-response relationship, the data were also fitted to a quadratic model, a linear–quadratic model and a linear–exponential model as shown in table 3. For all HD, the linear dose-response model fitted the data better than the quadratic model as demonstrated by the lower deviance value of this model. In addition neither the linear-quadratic nor the linear–exponential model fitted better than the linear model demonstrated by the non-significant p-values for the likelihood ratio tests. For IHD over the full dose range the linear–quadratic dose-response model was a marginally statistically significantly better fit than the linear model (p = 0.048). However, when an upper cumulative dose limit of 0.4 Sv was applied to the data the significant difference between these models was lost.

Because of the significant impact on the dose response relationship for the IHD risk, consideration should be given as why there is a drop in risk below the linear trend at cumulative doses above 0.4 Sv. Radiation workers in this cohort typically received only a small dose of radiation each year so it would take many years to accumulate doses of 0.4 Sv or more. Thus workers who accumulate such ‘moderate-to-high doses’ would be more likely to have been first employed at a younger ages, to have been employed in earlier decades, e.g. the 1950s–1970s, when annual doses were higher, and to have worked for a long period in the industry. The employment length for workers first employed later in life would be less and therefore may not be sufficient to accumulate to a high dose level, particularly if they had been employed in later decades. The reduced risk observed among this group of workers agrees with the results in table S1 which shows the numbers of deaths in both the higher dose group and employment length greater than 30 years were much smaller for the older age-at-first-exposure group. From the cross tabulation of deaths by age-at-first-exposure and cumulative dose categories in table S1, the proportions of deaths in each of the dose categories is similar for the <30 and 30–45 years age-at-first-exposure groups, but the percentage of deaths decreases rapidly as the cumulative dose increases for the 45+ years age-at-first-exposure group. This indicates that younger age-at-first exposure group received higher cumulative doses and contributed more numbers of deaths accordingly. For the cross tabulation of deaths by age-at-first exposure and employment length, it can be seen that the numbers of deaths drastically decreases after 20 years of employment for the age-at-first-exposure 45+ years group for both IHD and the group of other HD. For age-at-first exposure 30–45 years, a similar decrease in the number of deaths occurs after 30 years of employment. All of these facts suggest that younger workers were generally of better health and less susceptible to IHD, and hence demonstrate a relatively lower raised radiation-associated risk for IHD mortality after a long period of employment. Therefore the relatively lower ERR/Sv
at high cumulative doses in this cohort study may show a healthy worker survivor effect for IHD.

The healthy worker survivor effects can also be seen in the results of the analysis of risk related to employment status presented in table 8. The ERR/Sv decreased for workers who remained in the employment until close to the retirement age (within 5 years) for the age-at-first-exposure groups <30 years and 30–45 years. However, this healthy worker survivor effect is absent for the older workers first exposed above 45 years of age, because their employment was too short to reveal such effects.

In contrast to IHD, the ERR for other HD was significantly raised at cumulative doses greater than 0.4 Sv (table 2 and figure S2). This suggests that although some workers are employed for decades in the nuclear industry and demonstrate a relatively low radiation-associated risk for IHD, they are at higher risk for developing other HD potentially induced by radiation exposure. Nevertheless, the number of deaths from other HD was much smaller than that of IHD, and the contribution to overall HD mortality risk from other HD is small. This interpretation is also supported by the analysis of ERR/Sv versus employment length as shown in table 5 and figures S7 and S8, which show that radiation-associated risk decreased for IHD mortality but increased for other HD mortality when employment length was greater than 30 years.

Effects from other parameters

Cigarette smoking is a major risk factor for many non-cancer diseases, especially for HD. In the NRRW study, the possibility of confounding effects from smoking cannot be directly investigated since there are no smoking data available for the workers. However, no raised ERR/Sv for both lung cancer (ERR/Sv = 0.08; 95%CI: −0.38, 0.62) and chronic obstructive pulmonary disease (ERR/Sv = −0.62; 95%CI: −1.05, −0.07) which are diseases strongly associated with smoking have been seen in the most recent analyses of these diseases in the cohort (Haylock et al 2018). This indirect evidence suggests that cigarette smoking is unlikely to be a major positive confounding factor in this analysis of HD risk. It is also noted that the standardised mortality rate (SMR) analyses for circulatory diseases in NRRW-3 showed a significantly low SMRs value (Muirhead et al 2009b), suggesting that there is a generally low level of background risk factors in the NRRW cohort. Nevertheless, although absolute risk of circulatory diseases among the radiation workers was lower than general population, the ERR of radiation exposure is still observable among the radiation workers as we have seen in this analysis.

The dataset used for this analysis is based on the NRRW-3 dataset with additional 10 years of mortality follow-up. However, the dosimetry information was still the same as the NRRW-3 analysis. To fully utilise the mortality follow-up information, the minimum 10 years lagging was used for the analysis. Alternative dose lagging of 15 and 20 years have also been tested. Radiation-associated risk estimates tended to increase with 15 year-lag and then level off for HD and IHD, but continued to increase with 20 year lag for other HD, which suggests that exposure to radiation during earlier years might play an more important role in other HD compared to IHD.

Possible biological mechanism for IHD

IHD is an age-related disease and the mortality rate is much higher at older ages than at younger ages. Biological studies suggest that the underlying mechanism for atherosclerosis is associated with the senescence of endothelial cells in arteries of the heart (Minamino et al 2019).
Cells become senescent upon reaching the end of their replicative potential when the lengths of their telomeres shorten to a critical point following each cellular division. The senescent endothelial cells have increased capacity for monocyte attachment and trans-migration (Colden-Stanfield et al 1994, Wu et al 1994, Hallahan et al 1996, Ma et al 2010, Khaled et al 2012). Monocyte attachment and recruitment into the intima are two of several essential atherogenic steps. Therefore, the prevalence of these senescent cells could be associated with the severity of the plaques.

A recent biological study (Lowe and Raj 2014) showed that doses of ionising radiation can induce cellular aging through a mutation-independent mechanism. Endothelial cells can become senescent prematurely as a result of radiation exposure, and these cells are indistinguishable from those that have aged naturally. In senescent endothelial cells the promoter regions of the CD44 gene become demethylated, and the resulting proteins are highly expressed on the cell surface, making the cells adhesive to monocytes. Furthermore, it was observed that the junctions between endothelial cells are significantly weakened by irradiation (Kabacik and Raj 2017). This increases the permeability for monocytes and other macromolecules such as low density lipoprotein (LDL) to infiltrate the vessel wall and initiate atherosclerosis. The reason why cells senesce upon radiation exposure is presently unclear, but a recent report by Hewitt et al (2012) suggests that cells whose telomeres are damaged by radiation undergo senescence, presumably due to their inability to repair lesions at these chromosomal sites. This is supported by other biological observations (Bouffler et al 1993, 1996, 2001, Goytisolo et al 2000, McIlrath et al 2001). The results from these studies provide evidence which may support the radiation-associated risk in IHD observed in our analysis.

There was no raised radiation-associated risk for HD observed at cumulative doses below 0.1 Sv. At very low levels of radiation exposure (<0.05 Sv), a negative point estimate of ERR/Sv was observed, but it is difficult to conclude whether this is due to anti-inflammatory properties of low dose, because the negative risk estimate was not statistically significantly different from zero risk. It remains an interesting topic for both radiobiological and epidemiological studies, and the continued follow up of the NRRW cohort will provide more evidence concerning this important topic.

Limitations of this study

One of the sources of uncertainty is from dosimetry. Early dosimeters had high threshold detection limits and the assessment of neutron exposure in the first 20–30 years of follow-up was poor, although overall the neutron exposure is thought likely to make up only a small component of the total external exposure. A further drawback is the lack of quantitative internal dose estimates. Finally potential confounding lifestyle factors such as smoking, medical history such as diabetes, obesity, hypertension, high levels of blood LDL, and body mass index are not available.

Conclusions

Our analysis has shown a statistically significant increase in risk with cumulative external dose for overall HD mortality amongst UK radiation workers. For IHD mortality, the raised radiation-associated risk first appeared at least 20 years after first radiation exposure. There was no excess risk for cumulative dose below 0.1 Sv for IHD mortality. The dose response relationship showed that the radiation-associated risk decreases from the expected value.
derived from the linear trend at high doses above 0.4 Sv, this low ERR/Sv appears to be associated with workers who started employment at a younger age with a long employment lasting over 30 years and it may be due to the healthy worker survivor effect. This analysis provided further evidence that low levels of radiation exposure may be associated with an increased risk of IHD. Further follow-up of this cohort, taking into account potential confounders associated with lifestyle is required to derive more accurate radiation associated risk at low dose rate exposure, which is important in the field of radiological protection.

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