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Source: Radiation Research, 198(1) : 1-17

Published By: Radiation Research Society

URL: https://doi.org/10.1667/RADE-20-00269.1

RADIATION RESEARCH **198**, 1–17 (2022)
0033-7587/22 $15.00

DOI: 10.1667/RADE-20-00269.1

# Extended analysis of solid cancer incidence among the Nuclear Industry Workers in the UK: 1955–2011

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**Hunter N, Haylock RGE, Gillies M, Zhang W. Extended analysis of solid cancer incidence among the Nuclear Industry Workers in the UK: 1955–2011. Radiat Res. 198, 1–17 (2022).**

**Radiation worker studies provide direct estimates of cancer risk after protracted low-dose exposures to external X-ray and gamma-ray irradiations. The National Registry for Radiation Workers (NRRW) started in 1976 and has become the largest epidemiological program of research on nuclear workers in the UK. Here, we report on the relationship between solid cancer incidence and external radiation at the low-dose levels in 172,452 NRRW cohort members of whom (90%) were men. This study is based on 5.25 million person-years of follow-up from 1955 through the end of 2011. In the range of accumulated low doses two-thirds of workers have doses of less than 10 mSv. This study is an updated analysis of solid cancer incidence data with an additional 10 years of follow-up over the previous analysis of the NRRW cohort (NRRW-3). A total of 18,310 cases of solid cancers based on a 10-year lag were registered and of these 43% of the solid cancer cases occurred during the latest 10 years. Poisson regression was used to investigate the relationship between solid cancers risk and protracted chronic low-dose radiation exposure. This study demonstrated for solid cancers a rapid decrease of risk at high external doses that appeared to be driven by the workers who were monitored for potential exposure to internal emitters and who had also received relatively high external doses. Among cohort members only exposed to external radiation, a strong association was found between external dose and solid cancers (ERR/Sv = 0.52, 95% CI: 0.11; 0.96, based on 13,199 cases). A similar pattern is also seen for lung cancer. Excluding lung cancer from the grouping of all solid cancers resulted in evidence of a linear association with external radiation dose (ERR/Sv = 0.24, 95% CI: 0.01; 0.49, based on 15,035 cases), so suggesting some degree of confounding by smoking. Statistically significantly increasing trends with dose were seen for cancers of the colorectal, bladder and pleura cancer. Some of these results should be treated with caution because of the limited corroborating evidence from other published studies. Information on internal doses as well as non-radiation factors such smoking would be helpful to make more definitive inferences.** 

## INTRODUCTION

The International Commission on Radiation Protection (ICRP) bases its recommendations to protect workers and the public primarily on information about the long-term carcinogenic effects of radiation exposure derived from the Life Span Study (LSS) cohort of the Japanese atomic-bomb survivors in Hiroshima and Nagasaki. Solid cancer incidence in this LSS cohort was recently examined for a third time incorporating an additional 11 years of follow-up, updated dosimetry estimates and adjustment for smoking. For males, a linear-quadratic model with upward curvature was found to be the best description of the shape of the dose response, while for females a linear dose-response model remained best (1). Factors affecting this upward curvature in the LSS study were discussed in detail; not all site-specific cancer types may have the same curvature due to the involvement of different effect modifiers. The recent publication of the Japanese A-bomb survivors study emphasised that using a single background model for all solid cancer may not be appropriate (2). However, uncertainty remains about the applicability of risks derived from the LSS cohort to populations that have very different underlying risks of cancer and receive chronic low doses of radiation.

Studies of nuclear workers have the potential to give a direct assessment of the carcinogenic effects of protracted low-dose exposure. Data from several major radiation worker studies have been pooled at national and international levels, to provide greater precision in direct estimates of cancer risk. The International Workers Study (INWORKS) has carried out a combined analysis of mortality among combined nuclear industry workforces in France, the United Kingdom and the United States (3). The INWORKS cohort comprised 308,000 workers (mostly men) and anonymized data from the original third analysis of the UK National Registry for Radiation Workers

*Editor's note*. The online version of this article (DOI: https://doi.org/10.1667/RADE-20-00269.1.S1) contains supplementary information that is available to all authorized users.

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(NRRW-3) (4, 5) makes up a large proportion of the INWORKS (roughly half of the numbers). Workers were exposed mostly to X rays and gamma rays at low dose rates with an average duration of follow-up of approximately 26 years; the study found a linear increase in risk with dose for the grouping of all solid cancers (3). In the UK, NRRW-3 has shown an association between external exposure to ionizing radiation and the mortality and incidence from grouping of all malignant neoplasms excluding leukemia, consistent with risk estimates derived from the A-bomb survivor data (4, 5). A recent updated analysis based on the same NRRW-3 cohort with an additional 10 years of follow-up provided even more precise estimates of the risks of cancer mortality and cancer incidence following occupational radiation exposure and strengthens the evidence for raised risks due to protracted low-dose exposures (6).

The analyses performed in this study are complementary to and extend those undertaken in the recent updated NRRW-3 study which only examined evidence for a linear dose response relationship based on a fully stratified baseline model (6). Here, attention is focused on the analysis of the radiation risks of all solid cancer combined incidence as a single group. For the first time a parametric baseline model will be used, and various non-linear dose response functions used to the investigate the shape of the exposure-response relationship best supported by the data. The paper also examines temporal variation in radiation risk with age, time since exposure etc.

## MATERIALS AND METHODS

### *Study Design*

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 studies (4–6). The NRRW includes workers from a wide range of employer organizations, they are most of the nuclear industry in the UK; British Nuclear Fuels Ltd. (BNFL), Atomic Weapon Establishments (AWE), UK Atomic Energy Authority (UKAEA), British Energy Generations and Magnox Electric sites in England & Wales and Scotland, the Ministry of Defence (MoD), GE Healthcare, Rolls-Royce, as well as many smaller organizations in the research and industrial sectors from all parts of the UK.

The study population comprised monitored workers from these organizations for whom individual dose records were kept. Work histories of these cohort members were constructed using occupational records, including individual identifiers, name, date of birth, period of employment and industrial classification whether a worker was an industrial worker or not. The NRRW cohort contains data collected prospectively about workers in employment since 1976 when the study began, and data collected retrospectively on radiation workers employed since the beginning of the nuclear industry in the late 1940s. However, the data about workers employment prior to 1955 were excluded because of incomplete data issues (4, 5). Participation in the study is voluntary but less than 1% opt out.

Information on cancer registrations, mortality and emigrations of workers was obtained from the National Health Service Central Registers (NHSCRs), which are now maintained by NHS Digital for England & Wales, and for Scotland data were obtained from National Records of Scotland (4, 5). Cancer registration data has been in all parts of the UK since 1971 via regional cancer registries covering England, Wales and Scotland. The analysis of cancer incidence here was based on the earliest cancer mentioned on either a cancer registration or a death certificate. It includes all cancers registered and reported to the study during the period of follow-up which ended on 12/31/2011. Cause of death and cancer diagnoses were coded in accordance with the International Classification of Diseases (ICD)'s 9th revision (7). Only first primary cancers were considered although non-melanoma skin cancers (NMSC) were only registered as a censoring event. The following ICD-9 codes (140-172, 174-199) were included for all combined solid cancer incidence data analyses. In addition to all solid cancer groupings, risk in relation to 23 site specific cancer groupings were also considered. A cohort of 172,542 workers was analyzed here, which is essentially the same as that reported previously (4–6). The number of workers reported previously (6) is smaller than that quoted here because it represents the number of workers who contributed to the 10-year lagged analysis rather than the original cohort size.

### *Dosimetry*

The external dose estimates used here were identical to those in previous NRRW studies (4–6). For each radiation worker, employers supplied us with an annual dose of whole-body penetrating radiation. Most of the doses are associated with X rays and gamma rays and to a lesser extent beta particle and neutrons (4–6). Doses to the surface of the body were monitored using individual film badges (or personal monitors) and are expressed in sievert (Sv). As doses were recorded primarily to ensure compliance with dose limits or constraints, corrections were applied to arrive at more accurate dose estimates (4, 5). Some radiation workers have recorded neutron doses however the recording of neutron exposure did not start until the 1970s so workers employed prior to that time may have unrecorded exposures. Where neutron exposure information exists, it was added to the exposure from other sources.

Workers annual exposures in the early years of the UK nuclear programme were higher than in later years. The main contribution to the collective external dose comes from workers first employed in the 1950s (mean dose of about 77.7 mSv) and in general those workers had the highest lifetime external doses. Radiation workers first employed 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. However, the mean annual doses fell steadily and by the end of the 1990s it was down to 2.1 mSv although the number of workers monitored each year remained relatively constant from the 1970s through to the 1990s (4, 5).

Some workers were 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 available for the NRRW cohort. Where the study had been informed that workers were monitored for potential exposure to internal emitters this information was classified into two groups as monitored and unmonitored. Of the updated NRRW-3 cohort, 25% and 17% of male and female workers respectively were identified as being monitored for potential exposure to internal emitters. These workers tend to accumulate higher external doses and have longer lengths of service, longer exposure histories and are more likely to have worked in the early years when the average annual doses tended to be higher. Figure 1 shows the distribution of the cumulative external dose exposure according to workers internal monitoring status. The external doses received by workers monitored for internal exposure (mean dose 61mSv) were higher than those who were not monitored for internal exposure (mean dose 13mSv). It is also clear to see that the distribution of doses was highly skewed with a median dose of 3mSv overall and the mean cumulative dose was 24.9mSv (27.0 mSv for men and 5.6mSv for women).

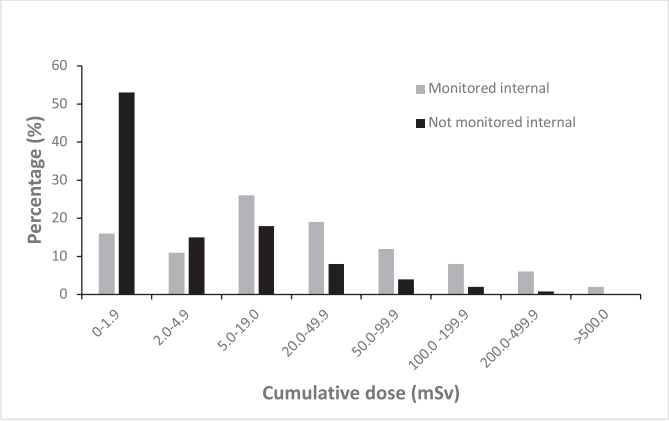


**FIG. 1.** Distribution of cumulative external dose according to internal monitoring status.

*Statistical Methods*

As in previous studies of this cohort (4–6, 8, 9) Poisson regression was used to conduct internal comparisons between solid cancer incidence and exposure to external radiation. For each worker, person-years at risk were accumulated over time from the date of start radiation work with a participating employer, date from which full dose data were available, or January 1, 1955, whichever occurred latest. The analyses here were based on a lag of 10 years, in which cases the follow-up commenced on the start of radiation work plus 10 years or January 1, 1955, whichever was later.

Follow-up ended on the date of the first cancer registration, date of death or emigration, their 85th birthday or December 31, 2011, whichever occurred first. The analyses here excluded cancers at ages of 85 years and over because of problems ascertainment at high ages.

Tabulations of person-years, cancer cases and summary variables were created using DATAB, a module of Epicure (10). Data were cross-classified by sex, attained age (14 categories by 5-year age intervals: 15–19, 20–24,. . .,80–85), calendar year categories (1955-, 1960-,. . .2010–2011), first employer group (15 groups), industrial classification (industrial/non-industrial/unknown), internal monitoring status (2 categories: monitored for internal radiation/non-monitored) and cumulative external dose in 13 categories (0-, 5-, 10-, 20-, 50-, 100-, 150-, 200-, 300-, 350-, 500-, 600- and 800+ mSv). To allow for a latent period in a radiation effect, as for previous NRRW analyses, cumulative exposures were also lagged by 10 years; the first 10 years of follow-up were excluded from analysis. This was allowed for a latency period between radiation exposure and disease onset.

Main analyses initially were based on a linear excess relative risk (ERR) model; relative risk (RR), that is the RR = ERR+1. The data were fitted to the following model [Model 1: $b_0$ (a, s, i, b, f, d) {1+β*dose}], where β is an estimate of the ERR and measures the increase in the ERR per unit increase in cumulative dose in Sv and $b_0$ is the background cancer incidence rate in the absence of radiation exposure (dose = 0) and depends on attained age (a), sex (s), birth cohort (b), industrial classification (i), duration of employment/exposure (d) and first employer (f). Fully parametric model was considered here for the background incidence rate as an alternative approach to our previous analyses of the NRRW cohort (4–6) that were used a non-parametric approach using stratified models (4–6). Allowance was made in the analyses to control for background factors affecting cancer risk using various parametric models by including covariates mentioned above in the model by adding them to the model and the improvement in fit was assessed by comparing the change in deviance to the Chi-squared distribution on the appropriate number of degrees of freedom. The final selected parametric model for the baseline risk is described in Eq. (1):

$$b_0 = \exp\{\alpha_s + \beta_s \log(a/60) + \lambda_s \log^2(a/60) + \gamma_s \log^2(a/60) I_{male>60} + s * i + s * b + male * f + male * d\} \quad (1)$$

The model includes industrial classification, which is correlated with socio-economic status (SES) and first employer group to account for geographical variations in cancer rates between different employers/sites. In addition, duration of employment/exposure was also added to the model to adjust for a possible ''healthy worker survivor effect'' (HWSE) using a two-level duration of employment that was classified as <30 and 30 or more years. Additional adjustment for a female specific first employer group factor did not have any significant effect on the overall result for solid cancers. These findings are not surprising because the number of cases among females was relatively small compared to that among male workers in these institutes. Adjusting the baseline model for a finer classification of duration of employment (<10, 10–19, 20–29, 30+ years) rather than a two-level factor or calendar time did not have any significant effect for the model.

Departures from the linear ERR model (Model 1) were examined by comparing the fit of a linear dose response model to that of a linear-exponential (LE: $b_0$ {(1+ $\beta_1$dose) exp($\beta_2$dose)}, and a linear-quadratic (LQ: $b_0$ {1+ $\beta_1$dose+ $\beta_3$dose$^2$} model. The improvement in the fit of these models, relative to the linear ERR model, was assessed using the likelihood ratio test statistic. Analyses were also conducted to evaluate factors that may modify the dose-response trend such as sex, attained age, age at first exposure, time since first exposure, duration of exposure and so on. The importance of differences in the ERR/Sv across levels of each modifying factors were assessed by comparing (Model 1) with the model: $b_0$ (1 + $\beta_j$*dose) (Model 2), where j denoted the number of index of categories of the modifying factor of interest.

A sensitivity analysis was conducted to assess the impact of those workers monitored for exposure to internal emitters on the main findings in relation to external dose. The workers were subdivided into two groups; those with only external exposure and those who were also monitored for potential internal exposure and the analyses repeated for each group. The sensitivity of the findings to the choice of lag period was also examined for 5, 15 and 20 years.

All the analyses were carried out using the AMFIT module in the EPICURE (10). Likelihood ratio tests and likelihood-based confidence intervals (CIs) were reported. P values relate to two-sided tests along with 95% CIs for the ERRs.

## RESULTS

The current analysis comprises 172,452 workers from the NRRW who were followed up until the end of 2011, of whom (90%) were men, and who accrued in total 5.25 million person-years of follow-up based on unlagged data. Only 12% of the workers had ever been employed by more than a single participating employer. The employer with most workers was the UK Ministry of Defence (MoD) with 37% of the cohort while 23% were employed by British Nuclear Fuels plc (BNFL) and 16% by the UK Atomic Energy Authority (UKAEA) (4–6). The mean duration of work at these organizations was between 5 and 15 years, and most of the workers (61%) started their employment aged less than 30 years (average 30 years for males and 27 years 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 years old.

**TABLE 1**
**Crude Incidence Rate by Sex, Employer Dose, Duration of Exposure and Internal Exposure of the NRRW Study Population (Unlagged)**

| | Total number of workers | Person years | Number of solid cancer cases | Crude solid cancer rate per $10^4$ | Mean cumulative dose (mSv) |
|---|---|---|---|---|---|
| Sex | | | | | |
| Male | 155,756 | 4,785,522 | 18,374 | 38.39 | 26.98 |
| Female | 16,696 | 467,397 | 1,368 | 29.27 | 5.56 |
| Employer | | | | | |
| British Nuclear Fuels plc (BNFL) | 40,071 | 1,256,556 | 5,342 | 42.51 | 53.7 |
| UK Atomic Energy Authority (UKAEA) | 27,502 | 954,727 | 4,120 | 43.15 | 34.0 |
| GE Healthcare | 3,871 | 101,472 | 290 | 28.58 | 31.1 |
| British Energy Generation and Magnox Electric Ltd (England and Wales) | 13,181 | 432,245 | 1,909 | 44.16 | 24.0 |
| British Energy Generation and Magnox Electric Ltd (Scotland) | 3,127 | 85,032 | 301 | 35.40 | 22.7 |
| Rolls-Royce Submarines | 3,265 | 92,306 | 289 | 31.31 | 14.7 |
| Research Organisations | 3,078 | 93,901 | 333 | 35.46 | 10.9 |
| Atomic Weapons Establishment (AWE) | 14,730 | 426,408 | 1,894 | 44.42 | 8.2 |
| Ministry of Defence (MoD) | 63,627 | 1,810,272 | 5,264 | 29.08 | 8.0 |
| Dose range (mSv) | | | | | |
| <10 | 117,382 | 4,413,454 | 11,866 | 26.89 | 2.06 |
| 10+ | 34,937 | 754,395 | 4,580 | 60.71 | 23.72 |
| 50+ | 9,727 | 194,272 | 1,510 | 77.73 | 70.13 |
| 100+ | 10,406 | 195,256 | 1,786 | 91.47 | 244.3 |
| Duration of exposure | | | | | |
| <30 years | 163,837 | 5,179,198 | 18,982 | 36.65 | 19.83 |
| 30+ years | 8,615 | 73,721 | 760 | 103.1 | 121.5 |
| Age-at-first exposure | | | | | |
| <25 | 69,878 | 2,295,730 | 2,825 | 12.31 | 20.2 |
| 25– | 32,651 | 1,209,281 | 4,003 | 33.10 | 26.3 |
| 30– | 37,372 | 1,087,202 | 6,497 | 59.76 | 31.3 |
| 40– | 32,551 | 660,706 | 6,417 | 97.12 | 26.2 |
| Monitored for internal exposure | | | | | |
| Yes | 42,257 | 1,341,300 | 5,419 | 40.40 | 61.25 |
| No | 130,195 | 3,911,619 | 14,323 | 36.62 | 13.11 |
| Total | 172,452 | 5,252,919 | 19,742 | 37.58 | 24.90 |

As of December 31, 2011, a total of 18,310 cases of all solid cancers were registered as their first primary cancers based on a 10-year lag. This number includes an additional 96 cases of solid cancer to that reported in a previous stratified analysis of this cohort (6) in which these cases were excluded because they only contributed information to uninformative strata. Among the 18,310 cases, 43.1% occurred during the latest 10 years (2002-2011) of added follow-up since the previously reported study (4, 5). About 93% of the solid cancers occurred in male workers and approximately 74.2% of all cases occurred above 60 years of age. The mean age at diagnosis for solid cancers was 64.8 years (for male 65.3 and female 57.8 years). Overall, about 10.5% of the workers had a solid cancer registered but the percentage varied by employer and ranging from 6.5% (GE Healthcare) to 14.2% (UKAEA). Just over a quarter (28%) of all solid cancer cases were among workers monitored for internal exposure and 204 of these cases were among women.

The crude solid cancer incidence rate also varied between employers, ranging from 28.6 (GE Healthcare) to 44.4 (Atomic Weapons Establishment, AWE) per $10^4$ person years (Table 1). The rates for males were higher than those for females and were also higher for those workers employed for more than 30 years compared to those employed for less time. Incidence rates increased with increasing age at first exposure. The mean cumulative dose was varied considerably between employers; the highest mean lifetime doses arise for BNFL employees (53.7 mSv), followed by UKAEA (34.0 mSv) and GE Healthcare (31.1 mSv). The distribution of the period of birth of the workers showed a peak for births between the late 1940s and the early 1960s (Table S1; https://doi.org/10.1667/RADE- 20-00269.1.S1). Mean lifetime doses are largest for those born in the earliest cohort.

### *Solid Cancer and Radiation Risk Analysis*

Examinations were made of how baseline solid cancer rates (in the absence of radiation) varied by gender, age and other non-radiation risk factors. The rates increased significantly with attained age among both men and women; they increased in proportion to the eighth power of attained

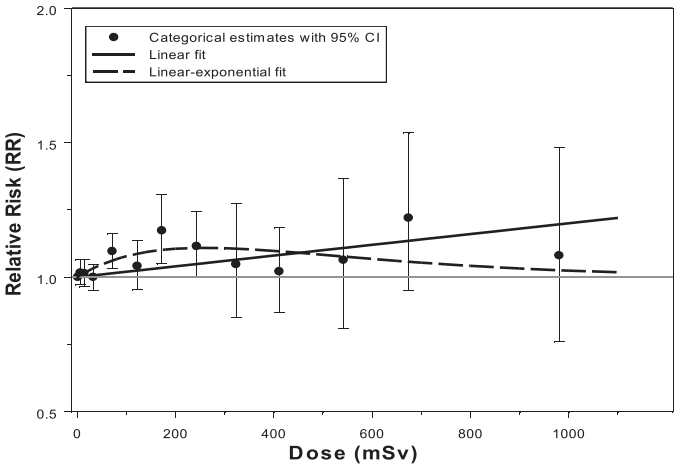


**FIG. 2.** Dose-response functions for all solid cancers combined having adjusted for background non-radiation factors. The grey horizontal solid line represents a RR of 1. Covers all exposures, the category-specific estimates with 95% confidence intervals (CI) and the risk estimates based on linear and LE non-linear models. (Lagged by 10 years.)

age in males and to the fourth power in females and the rate decreased at older ages both sexes. There was strong evidence of a difference in baseline rates between industrial and non-industrial workers ($P < 0.001$) for both men and women; the rate was significantly higher among industrial workers by approximately 19% and 22% relative to non-industrial workers for males and females, respectively.

Cancer incidence rates also increased by about 2% for males and 9% for females per decade increase in birth year while the incidence rate, particularly for males, was slightly lower among those who worked 30 years or more compared to those who worked less than 30 years. There were statistically significant differences in the baseline incidence rates of solid cancer by the first employer among males ($P < 0.001$). The rate was statistically significantly higher at the UKAEA site at Dounreay (15%), BNFL site at Sellafield (14%), Scottish nuclear power stations (14 %), MOD (13%) and AWE (8%) relative to male workers at the combined UKAEA sites (Harwell and other sites).

One of the distinctive features of this study was that workers were exposed to protracted low-dose radiation exposure; two-thirds of workers experienced doses of less than 10 mSv while only 6% of workers accumulated doses of more than 100 mSv, and this later group contributed nearly 60% of the collective dose in the study population. Only 70 workers had recorded doses more than 1 Sv over their working lifetime.

The results of the analysis of the relationship between solid cancer risk and cumulative external doses are shown in Fig. 2, together with 13-dose category specific relative risk estimates. There was some evidence of a statistically significant increasing linear trend for all solid cancers ($P = 0.05$) with an ERR/Sv of 0.20 (95% CI: -0.001; 0.43), having adjusted for the background risk (Eq.1). While the linear dose response model appears to be a reasonable approximation of excess risk over the whole dose range, it generally underestimates risk at lower doses and overestimates risk at higher doses (Fig. 2). A linear-exponential (LE) model provided a better fit than that of the linear model ($P = 0.01$) but the evidence for a better fit of a linear-quadratic (LQ) model over the linear model was much weaker ($P = 0.086$). The shape of the LE model better reflected the apparent levelling off and even downward trend in the overall relative risk per unit dose at the high cumulative exposures; the linear-exponential model contains a positive linear term of ERR/Sv of 1.14 (95% CI: 0.30; 2.36) and an exponential term of exp(ERR/Sv) of –3.86 (95% CI: –9.07; –0.81). However, the evidence for non-linearity (based on LE model) disappeared when the data were limited to cumulative exposures to below 400 or 200 mSv ($P = 0.11$, $P > 0.50$, respectively). The ERR/Sv estimates over the following restricted dose range were: 0–400 mSv (ERR/Sv = 0.41, 95% CI: 0.08; 0.76, $P = 0.01$, $N = 18{,}007$) and 0–200 mSv (ERR/Sv = 0.82, 95% CI: 0.31; 1.36, $P = 0.001$, $N = 17{,}486$ cases). The lowest dose range showed good evidence of a linear dose response was at 0–100 mSv with an ERR/Sv estimate of 0.98 (95% CI: 0.14; 1.86, $P = 0.02$, $N = 16{,}524$ cases). The risk estimates increased, and the associated CIs widened as the dose range decreased.

Analyses were also carried out to look for evidence that any factors would modify the excess relative risk per unit dose based on the linear model (Table S2; https://doi.org/10.1667/RADE-20-00269.1.S1). There were no statistically significant variations in the ERR/Sv with sex ($P > 0.5$), industrial classification ($P > 0.5$) or attained age ($P = 0.49$). The risk for internally monitored workers was three times lower than that for unmonitored (i.e., external radiation) workers, although there was no evidence of heterogeneity in the dose response ($P = 0.14$). However, a test of heterogeneity indicated a statistically significant effect of the four-level age at first exposure factor ($P = 0.04$), but when a two-level factor (<30 and 30+ years) was considered, a little more than half of the cases (64%) started work at age 30 years and older, the test for heterogeneity provided more substantial evidence of a difference ($P = 0.007$); workers who were older at initial exposure were estimated to have greater risk with an ERR/Sv of 0.39 (95% CI: 0.14; 0.67) compared to those exposed from younger ages with an ERR/Sv of –0.07 (95% CI: –0.32; 0.214). There was borderline evidence for the ERR/Sv decreasing with increasing duration of exposure ($P = 0.05$). Implementing alternative lag periods made little difference to the risk estimates (Table S2) and the dose response remained best described by the LE model (estimates not shown here).

### *Individual Site-Specific Cancers*

We also investigated 23 non-overlapping different cancer sites based on whole-body dose lagged by 10-years. The

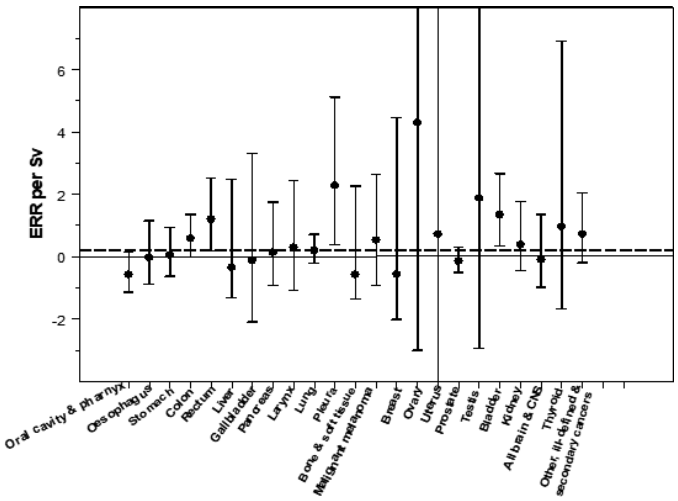


**FIG. 3.** Excess relative risk per (ERR/Sv) with 95% CI for incidence of specific solid cancers and all solid cancers combined based on lagged by 10 years (the horizontal dashed line is the overall ERR/Sv of 0.20; solid line represents an ERR of 0).

results including RR estimates for various dose categories were (<20 mSv, 20–50 mSv, 50–500 mSv and 500+ mSv) and the linear ERR/Sv are presented in Table S3 (https://doi.org/10.1667/RADE-20-00269.1.S1). Prostate and lung cancers were the most common cancers among males and accounted for about 22.0% and 19% of cases, respectively, while the breast was the most common site for cancer among females (42%). Among the 3,818 prostate cancer and 3,163 lung cancer cases in males, about 59% of the prostate and 29% of the lung cancer cases were recorded during the latest 10 years of follow-up. For females, of the 515 cases of breast cancer and 112 cases of lung cancer, about half of these cases were recorded between 2002–2011. Other commonly occurring sites of cancer included the colon (9.0%), bladder (6.6%) and rectum (6.2%) among males, and lung (9.4%), uterus (9.4%) and colon (6.4%) among females.

For the analysis of each specific cancer site, same parametric baseline model was used as for the main solid cancer analysis (Eq. 1) unless otherwise indicated (Table S3; https://doi.org/10.1667/RADE-20-00269.1.S1). Figure 3 displays the linear trend estimates (ERR/Sv) and 95% CI for each cancer site while the dashed horizontal line represents the linear estimate of all solid cancers combined. Of the 23 non-overlapping grouping of cancers, 15 showed a positive point estimate of the linear trend. The RR increased with increasing dose for the cancer of colon, rectal, pancreas, pleura, malignant melanoma, and bladder, although strong evidence for a trend with dose was only observed for rectal ($P = 0.01$), pleura ($P = 0.01$) and bladder cancer ($P = 0.005$) and the weak evidence for colon cancer ($P = 0.06$).

### *Lung Cancer*

Because of increased interest in the possible effects of radiation exposure on lung cancer from low-dose studies, lung cancer was studied in more detail than in previous NRRW analyses. The results are shown in Fig. 4 (left panel). The dose category specific RR estimates showed a clear increase up to 400 mSv but dose groups above that value showed no raised risk but were based on only 1.6% of the total lung cancer cases. There was no evidence of increased risk for lung cancer with dose based on a linear dose response model (ERR/Sv = 0.16, 95% CI: –0.27; 0.70, $P > 0.5$) based on 3,275 cases, but strong evidence of a non-linear trend was found based on the LE model which provided a significantly improved fit ($P < 0.001$) however the LQ model did not provide a better fit over the linear model ($P = 0.30$). Lung cancer was much more common in males than in females in this dataset; for males the LE model also fitted significantly better than the linear model (a positive linear term of 5.14 and an exponential term of –7.14), but for females there was no evidence of a trend in risk with dose and

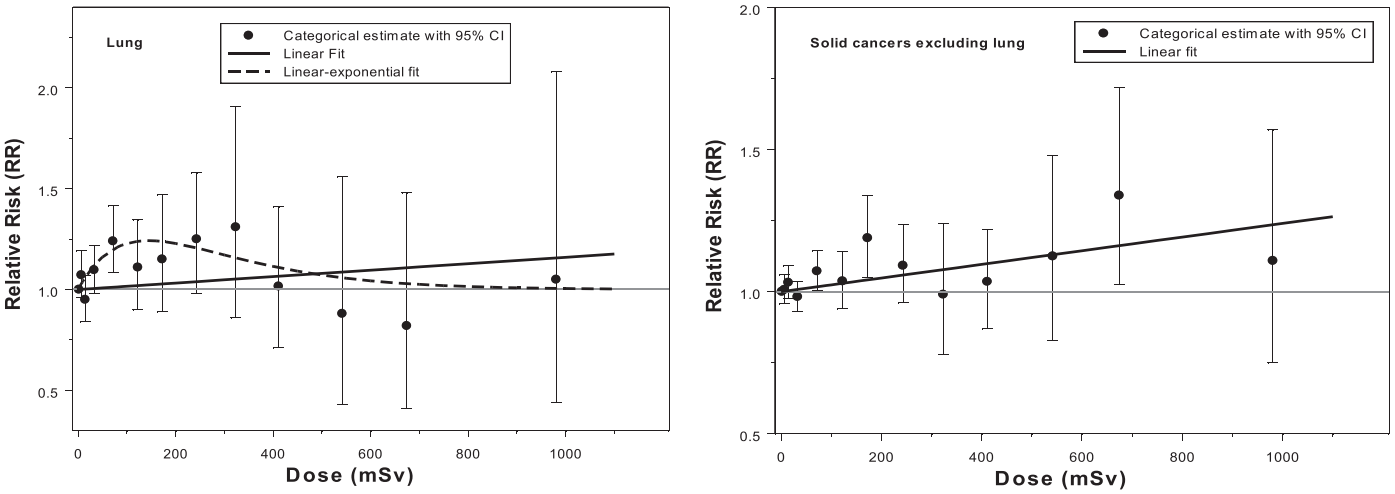


**FIG. 4.** Dose-response relationship for all radiation workers from lung cancer (left panel) and from solid cancer excluding lung (right panel) (Lagged by 10 years.)

the linear risk estimate was similar to the linear estimate observed from the LE model for males (ERR/Sv = 4.76). However, when the data were restricted to cumulative doses less than 400 or 200 mSv the lung cancer risks were best described by a linear-dose response relationship and the estimate of 0–400 mSv (ERR/Sv = 1.01, 95% CI: 0.23; 1.91, P = 0.01) and 0– 200 mSv (ERR/Sv = 1.51, 95% CI: 0.26; 2.91, P = 0.016) based on 98.5% and 94.7%, respectively, of the total lung cancer cases. The narrowest dose range to provide good evidence for a linear trend in the lung cancer risk was 0–100 mSv (ERR/Sv = 3.10, 95% CI: 1.01; 5.43, P = 0.003, based on 2,918 cases).

Temporal variation in the effect of exposure was also examined for lung cancer based on a linear model (results not shown). Neither gender (P = 0.22), attained age (P = 0.45) nor time since exposure (P = 0.26) were found to be effective modifiers of the risk. There was also no evidence of any heterogeneity in the dose response between unmonitored and monitored for internal radiation workers (P > 0.50), although the risk for monitored workers was lower (ERR/Sv = 0.14, 95% CI: –0.29; 0.71) than external radiation workers (ERR/Sv = 0.23, 95% CI: –0.68; 1.30). However, there was evidence of decreased risk with duration of employment (P = 0.04); indicating lower risk among those involved in radiation work for 30 or more years compared to a shorter duration. The ERR/Sv increased significantly with increasing age-at-first exposure (P = 0.02) as in the main analysis with the risk was lower for those start at a young age (<25) when compared with older ages as in the main analysis from solid cancer.

### *Solid Cancer Excluding Lung*

The change in the pattern of excess risk above 400 mSv observed for lung cancer suggests that the findings from lung cancer may be influencing the overall result for solid cancers. Thus, further analysis was carried out looking at the grouping of all solid cancers excluding lung cancer, which reduced the number of cases by around 18%.

Baseline solid cancer rates were also examined for solid cancers excluding lung. The rate is changed in comparison with the rate that of all solid cancers; the increasing rate for industrial workers was lowered by half (increased was only 6% and 13% for men and women, respectively, relative to non-industrial workers). However, cancer incidence rate was higher for birth cohort (increased was 10% for both men and women per decade increase in birth year). In addition, increased incidence rate was also reduced by half for among male workers at the UKAEA in Dounreay (7%), at the MOD (8%) and at the BNFL Sellafield site (8%) relative to male workers at the combined UKAEA sites (Harwell, Culham, Sellafield and other sites).

Excluding lung cancer from solid cancer led to a change in the best fitting dose response model. There was good evidence for an increasing linear trend with dose in the risk of solid cancer incidence other than lung with an ERR/Sv of 0.24 (95% CI: 0.01; 0.49, P = 0.04) based on 15,035 cases as shown in Fig. 4 (right panel). Fitting a LE trend provided no improvement over the linear trend (P = 0.16) or LQ trend (P = 0.14). Further analysis was also carried out to evaluate the effect of restricting the dose range. For the range of 0-200 mSv, the linear ERR/Sv remained statistically significant (P = 0.01), but the point estimate of the slope was larger (ERR/Sv= 0.75, 95% CI: 0.18; 1.34, N = 14,382). However, restricting cumulative doses to less than 100 mSv provided no evidence of a linear trend with dose (ERR/Sv = 0.62, 95% CI: –0.29, 1.59, N = 13,606, P = 0.19).

Further analysis was also conducted to examine the temporal variations and the results of the effect of modifying factors on the linear ERR/Sv estimates are shown in Table S2 (https://doi.org/10.1667/RADE-20-00269.1.S1). There were no statistically significant variations in the ERR/Sv with sex (P = 0.45), industrial classification (P > 0.5), attained age (P > 0.50) or whether a worker was monitored for internal emitters (P = 0.10), but again the risk estimate for monitored workers was about 3 times lower than that external radiation workers. There was also a lack of evidence that risk varied significantly between age at first exposure groups (P = 0.26) or duration of employment (P = 0.22). Implementing alternative lag periods made little difference to the risk estimates (Table S2; https://doi.org/10.1667/RADE-20-00269.1.S1).

### *Sensitivity Analysis*

The sub-cohorts of those workers who only experienced external exposure and those who were additionally monitored for internal exposure were examined separately for all solid cancers combined, lung cancer and solid cancer excluding lung. The results are shown in Table 2 and in Fig. 5.

For the external radiation worker sub-cohort, there was clear evidence for a linear association between cumulative external dose and the risk of all solid cancers combined (ERR/Sv = 0.515, 95% CI: 0.11; 0.96, P = 0.012). However, for the internally monitored sub-cohort, a LE dose-response model described the data better than the linear model (P = 0.01), both trends are also shown in Fig. 5. As a result, the significant LE pattern observed for all radiation workers in solid cancer appeared to be particularly influenced by those workers monitored for internal exposure, although only 28% of the total solid cancer cases occurred in that group.

The lung cancer cases were divided 67% among the external radiation workers and 33% among the internally monitored workers. In both these sub cohorts a pattern of reduced risk for cumulative external doses above 400 mSv was seen (Fig. 5). For the externally exposed workers the categorical point estimates increased with dose up to 300 mSv but the linear trend across the whole dose range was not statistically significant (ERR/Sv = 0.76, 95% CI: –0.31; 2.06, P = 0.18). However, this result was likely influenced

**TABLE 2**
**The Risk Estimates from the Best Fitted Model in Relation to External Dose for all Radiation Workers and Separately for External Radiation Worker and Monitored for Internal Exposure Sub-Cohort from Solid Cancers Combined, Lung Cancer and Solid Cancer Except Lung (Lagged by 10 years)**

| | Solid cancer | | Lung cancer | | Solid cancer excluding lung cancer | |
|---|---|---|---|---|---|---|
| | Cases | Best estimate (95% CI) | Cases | Best estimate (95% CI) | Cases | Best estimate (95% CI) |
| Main | 18,310 | $\beta_1 = 1.14$ (0.30; 2.36) $\beta_2 = -3.86$ (–9.08; –0.81) | 3,275 | $\beta_1 = 4.90$ (2.04; 9.00) $\beta_2$=-6.80 (–12.4; –3.54) | 15,035 | B = 0.24 (0.04; 0.45) |
| External radiation workers (sub-cohort) | 13,199 (27)* | $\beta = 0.515$ (0.11; 0.96) | 2,198 (1)* | $\beta$ =0.76 (–0.31; 2.06) | 11,001 (26)* | B = 0.53 (0.09; 1.02) |
| Monitored for internal exposure (sub-cohort) | 5,111 (144)* | $\beta_1 = 2.24$ (0.42; 4.83) $\beta_2 = -5.82$ (–12.7; –1.86) | 1,077 (26)* | $\beta = -0.11$ (–0.47; 0.44) | 4,034 (118)* | $\beta_1 = 2.01$ (0.21; 4.88) $\beta_2 = -4.55$ (–12.3; –0.32) |

*Notes*. Linear-exponential model: $\beta_1$ = linear term and $\beta_2$ = exponential term. Linear model (ERR/Sv): $\beta$ = linear term. *Total number of cases above 0.5 Sv.

by a single case with a cumulative dose above 500 mSv. When the dose range was restricted to less than 500 mSv then the central estimate of slope of the linear trend increased and became statistically significant (ERR/Sv = 1.33, 95% CI: 0.13; 2.77, P = 0.03). For the sub cohort of workers who were monitored for internal exposure, there is no clear pattern in categorical risk estimates and there was no evidence of a trend in risk with external dose (ERR/Sv= –0.11, 95% CI: –0.47; 0.44, P > 0.50).

For solid cancers excluding lung, 73% of the cases were among the sub-cohort of those only externally exposed and 27% among those also monitored for internal exposure. The dose category specific risk estimates for the external radiation workers sub-cohort show a clear increasing trend apart from the highest category where the risk is only slightly raised although this estimate is based on only 4 cases (Fig. 5). Overall, there was good evidence for a linear trend (ERR/Sv = 0.53, 95% CI: 0.09; 1.02, P = 0.04). For the sub-cohort of internally monitored workers, the pattern remained similar to that for all solid cancers. The LE model remained a statistically significantly better fit than the linear model (P = 0.04).

## DISCUSSION

Analyses of historical worker cohorts such as the NRRW are an important source of direct evidence to confirm and refine our understanding of cancer risks associated with radiation exposure especially at low-cumulative doses and low doses rates. Such studies enable changes in radiation risk with age at first exposure and over time to be assessed more fully and improve the risk models used to predict the lifetime risk from radiation exposure which form the basis of the regulations that protect workers and the public.

The statistical precision of the analyses performed here was improved over those previously reported (4, 5) as the follow-up has been extended by 10 additional years during which time the surviving proportion of the cohort remaining alive had reduced by 6.6% and 8,040 new solid cancer incidences were recorded which increases the power of the study to inform on radiation risks. This analysis differs from those previously undertaken in that it is the first to use a parametric baseline model, the first to investigate the shape of the dose response relationship and to examine the temporal variation in radiation risk for solid cancers.

### *Solid Cancers*

Over the whole dose range, and based on the whole cohort, the dose response relationship for all solid cancers incidence was best described by a linear-exponential function. The risk increased approximately linearly at low doses but flattened and started to reduce above a cumulative exposure of 400 mSV. However, only a small proportion (1.6%) of the total number of solid cancers occurred above 400 mSv. Furthermore, 84% of these cases occurred among workers who were monitored for internal emitters and of these 71% were employed at the BNFL-Sellafield site and worked longer (more than 20 years). Therefore, this LE function may not provide a reliable description of external radiation risk for the average worker.

The study showed that for the sub-cohort of externally exposed workers the dose response for solid cancer was linear. Whilst among the sub-cohort of workers who were also monitored for internal exposure, and who experienced 28% of the solid cancer incidences, the LE dose response model provided a better fit overall. This finding suggests that the LE dose response, which exhibits a downward curvature in risk at high doses for solid cancers is driven by the sub-cohort of workers monitored for internal exposure, in particular by those with cumulative exposure above 300 mSv (366 cases). Therefore, Table 3, presents a range of

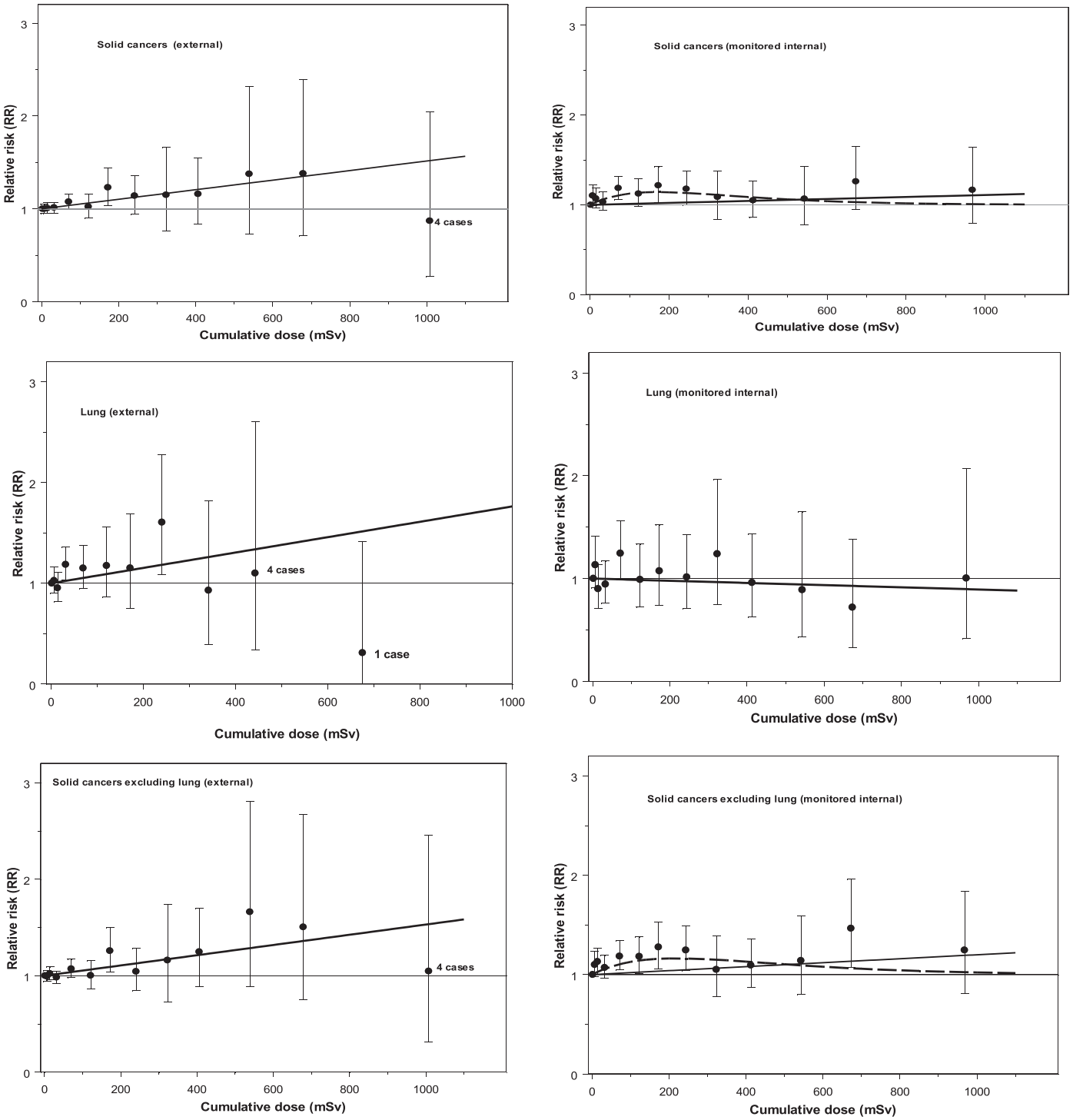


**FIG. 5.** Dose-response relation from all solid cancer combined, lung cancer and solid cancer excluding lung for the sub-cohort for external workers and for those workers potentially monitored for internal exposure (Lagged by 10 years.)

risk estimates from this study to compare with those from other studies and these estimates are also shown in Fig. 6a.

There appears to be reasonably good agreement, in that the confidence intervals overlap, between the range of estimates provided by this study and both the A-bomb survivors study (1) and the INWORKS study (3) although given this later cohort contains a significant part of the original NRRW-3 cohort some similarly would be expected. The risks derived here are larger than those for both mortality and incidence from the Mayak cohort (11, 12) even though the Mayak estimates exclude lung cancer and so reduce possible differences caused by variation in smoking rates between the cohorts and any impact of internal exposures of the lung.

**TABLE 3**
**Comparison Estimates of the ERR/Sv at 1 Sv/Gy for Radiation Exposure among Published Studies (Lagged by 10 Years)**

| | Study period | No. of study population | Mean recorded dose | Solid cancers | | Lung cancer | |
|---|---|---|---|---|---|---|---|
| | | | | No. of deaths/cases | ERR/Sv (95% CI) | No. of deaths/cases | ERR/Sv (95% CI) |
| Present updated NRRW-3 workers study (UK) | | | | | | | |
| Incidence | 1955–2011 | 172,452 | 24.9 mSv | 13,199 | 0.52 (0.11; 0.96) [1] | 3,225 | 1.01 (0.23; 1.91)[4] |
| | | | | 18,007 | 0.53 (0.09; 1.02) [2] | 2,198 | 0.76 (–0.31; 2.06)[1] |
| | | | | 15,035 | 0.24 (0.04; 0.45) [3] | 2,197 | 1.33 (0.13; 2.77)[5] |
| | | | | | 0.41 (0.08; 0.76) [4] | | |
| INWORKS (workers combined study in France, UK and U.S.) | | | | | | | |
| Mortality (3) | 1944–2005 | 308,297 | 25.2 mSv | 17,957 | 0.33 (0.12; 0.56) [#] | 5,802 | 0.51 (0.00; 1.09) [#, f] |
| | | | | | 0.32 (0.07; 0.60) [*, #] | | |
| | | | | | 0.47 (0.18; 0.79) [#, a] | | |
| | | | | | 0.20 (-0.03;0.45) [#, a, b] | | |
| Mayak PA workers study (Russia) | | | | | | | Mortality (14, 15) |
| Incidence (11) | 1948–2004 | 22,366 | 510 mSv | 1,447 | 0.07 (0.01; 0.19) [c] | 930 | 0.64 (0.45; 0.84) [f] |
| Mortality (12) | 1948–2008 | 25,757 | 350 mSv | 1,825 | 0.12 (0.03; 0.21) [c] | 789 | 0.40 (0.23; 0.57) [f, g] |
| | | | | | | 930 | 0.19 (0.07; 0331) [f, h] |
| Japanese A-bomb survivors study | | | | | | | Incidence (13) |
| Incidence (1) | 1958–2009 | 105,444 | 200 mGy [a] | 22.538 | 0.20 (0.12; 0.28) [d] | 2,446 | 0.83 (0.58; 1.09) [f] |
| Mortality (3) | 1950–2003 | 86,611 | | 10,929 | 0.32 (0.01; 0.50) [e] | 1,445 | 0.34 (0.14; 0.58) [f, i] |
| | | | | | | 2,446 | 0.65 (0.19; 1.21) [f, j] |

[1] External workers sub-cohort; [2]External workers sub-cohort and excluding lung; [3]For all workers excluding lung; [4]For all workers restricted doses 0–400 mSv; [5]External workers sub-cohort restricted 0–500 mSv.

[#] 90% CI. *Excluding lung.

[a] Based on colon dose; [b]All cancer excluding ionizing with no adjustment for neutron monitoring; [c]Excluding lung, liver and bone; [d]The ERR/Gy at 1 Gy for males linear quadratic model; [e]Male survivors exposed at ages 20–60 years; [f]lung dose; [g]Adjusted for plutonium internal dose; [h]Adjusted for plutonium internal dose + smoking; [i]For male workers only (at age 70 after radiation exposure at age 30); [j]For non-smokers, restricted 0–1 Gy, adjusted smoking (at age 70 after radiation exposure at age 30).

*Lung Cancer*

The analysis of lung cancer shows that the LE model is best fitting to all the data. However, the categorical risk estimates show a strongly increasing linear risk up to 400 mSv with very little risk above this cumulative external dose. When the workers who were monitored for internal exposures were examined separately there was no evidence for any external radiation dose response relationship at all for lung cancer. In contrast, among the sub-cohort of workers who were only externally exposed there was a stronger linear dose response relationship up to 500 mSv

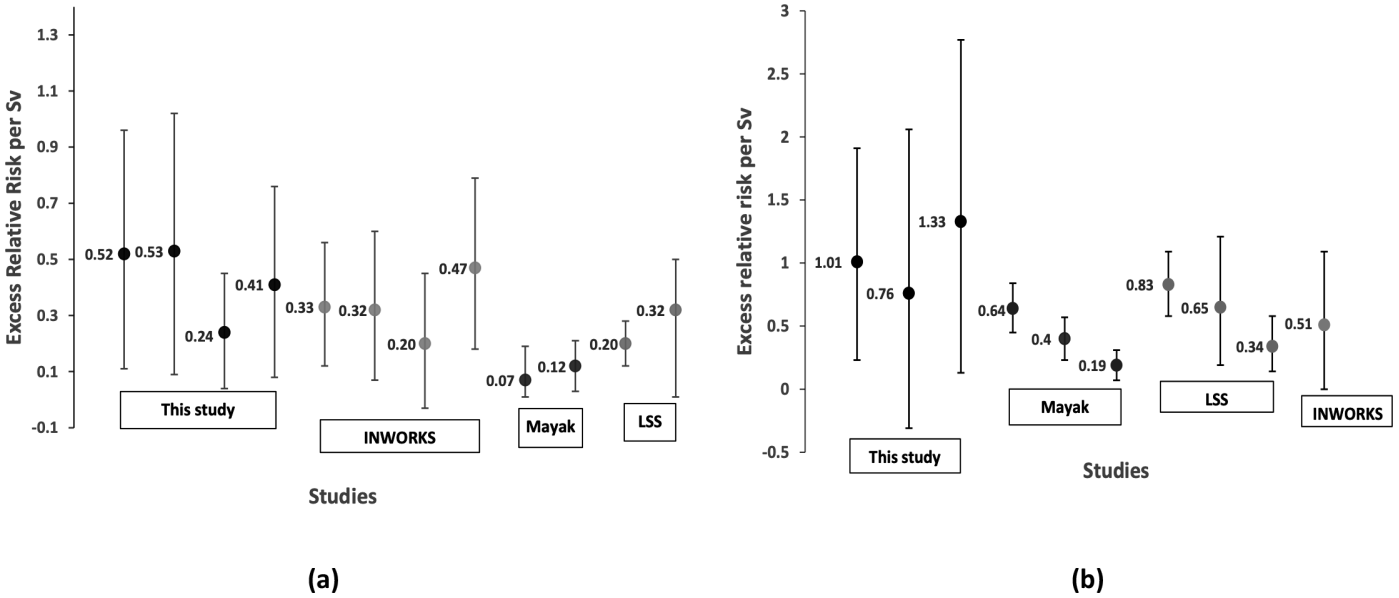


**FIG. 6.** Comparison of various estimates of the ERR/Sv at 1 Sv or 1 Gy for radiation exposure among published studies (lagged by 10 years): panel a, solid cancer; panel b, lung cancer.

but not above this (above 500 mSv there was only a single case).

Table 3 and Fig.6b shows the estimates from this work and together with the corresponding estimates from the Japanese A-bomb survivors, Mayak and INWORKS. In this study, for the external radiation worker sub-cohort, there was good evidence for a linear dose response over the range 0–500 mSv. Our estimates are generally consistent with the sex averaged ERR/Gy of 0.83 (95% CI: 0.58; 1.09) lung cancer incidence reported for the A-bomb survivors when smoking history was ignored (13). However, the male specific risk estimate from the A-bomb survivors' analysis is a lot lower (ERR/Gy = 0.34, 95% CI: 0.14; 0.58) than our NRRW estimates where the cohort is 90% male. A recent analysis of the Mayak cohort (14) shows a linear ERR/Gy for lung cancer mortality in relation to external dose with the sex averaged ERR/Gy of 0.64 (95% CI: 0.45; 0.84) based on unadjusted for smoking and plutonium exposure. When adjustment was made for both plutonium exposure and smoking, the ERR/Gy for external exposure was 0.16 for males and 0.55 for females (14). When comparing Mayak and NRRW risk estimates it should be noted that the average external doses for the Mayak PA radiation workers are an order of magnitude higher (455 mGy) than the NRRW cohort (24.9 mSv) and similar to that of Japanese A-bomb survivors. The Sellafield workers study (15), which is part of this NRRW data, also reported a reduction in risk for external dose after adjusting for plutonium exposure (ERR/Sv = 0.22, 90% CI: –0.25; 0.82, N = 409 deaths. Again, it should be noted that the average lung dose from plutonium among the Sellafield workers cohort (5.5 mGy) is far lower than that among the Mayak workers (175.6 mGy). The INWORKS study (16) reports a value of lung cancer mortality ERR/Gy of 0.51 (90% CI: 0.00; 1.09) based on 5,802 deaths without adjusting for smoking but does include workers monitored for internal exposure. Our estimates are based on a relatively large number of cases, but the estimates are larger, and the confidence intervals are wider than those published studies (13–16) but encompass those estimates (Fig. 6b), bearing in mind that those published estimates are based on organ dose to lung, while this NRRW study has used recorded doses or dose equivalent. Dose to lung is smaller than the recorded dose, e.g., the INWORKS reported that the lung dose could be 31% lower than recorded dose (17).

A joint analysis of lung cancer mortality based on the combined data of the three European nested cases-control studies (Belgian, French, and UK nuclear workers) (18) reported no evidence of a dose response relationship for external radiation dose after adjusting for internal doses, smoking and SES (ERR/Gy = −0.40, 90% CI: −0.58; 0.06, N = 553 cases). This risk estimate in the European study remained the same when the adjustment for internal dose was removed. Low statistical power due to small number of deaths or that external risk is independent of internal dose or that the internal doses were small may explain the lack of evidence in this study. There have also been several other individual nuclear workers studies that did not also show any increase in lung cancer with external dose, but these were also based on small numbers of deaths (19, 20).

### *Solid Cancers Excluding Lung Cancer*

The pattern of excess risk observed for lung cancer, in particular, the lack of excess risk above 400 mSv may be influencing the overall result for solid cancers. When all the data for solid cancers excluding lung were modelled together a linear dose response was best fitting. However, when workers who were internally monitored were considered separately there was a clear flattening of the increase in risk above about 100 mSv which lead to the LE model being the best fit. When the dose range was restricted to 0–300mSv then a linear-dose response was best fitting (P = 0.015) based on 3747 cases (ERR/Sv = 0.86, 95% CI; 0.16; 1.66) but as this was a broad disease category there were 287 cases over 300 mSv which means the fit over the whole dose range was not unduly influenced by only small numbers of cases at high doses. The best fitting model for the sub-cohort of workers only exposed to external radiation was clearly linear with no indication of a drop in risk at higher doses (85 cases were above 300 mSv).

Thus, we have good evidence for a linear dose response among the external workers over the full dose range and among the workers monitored for internal exposure but for this later group while there is clearly raised risk at cumulative doses above 300 mSv the pattern is unclear.

The INWORKS (3) which also found good evidence of elevated risk for solid cancers other than lung and the points estimate is in good agreement with our overall result (Table 3). However, the risk estimates for excluding lung, liver and bone from the Mayak (11, 12) are lower than our risk estimates (Table 3).

### *Potential Factors Affecting the Observed Dose-Response Relationships*

The obvious difference between workers who only have external exposures and those who are additionally monitored for internal exposures is the potential additional internal exposures these workers may have experienced. Currently the NRRW does not have any internal exposure data which means assessing if the size of the internal dose received is important is difficult. However, there may be an impact on the external dose response of simply being monitored for internal exposure. Internal workers tend to have much longer employment periods than external workers and these internally monitored workers make up a substantial proportion of the workers with higher external doses in the study population, e.g., about 84% of workers with doses over 400 mSv using unlagged data.

The HWSE is a potential cause of a reduction in risk per unit dose at higher cumulative exposures in that workers who continue to be healthy tend to remain in employment

longer and therefore accumulate larger doses. Epidemiological studies of various occupational groups including in the nuclear industry in many other countries have shown a HWSE (21, 22). The flattening of risk for solid cancers excluding lung above around 300 mSv among monitored internal radiation worker sub-cohort may be an example of this effect. In contrast, the external radiation workers who are generally employed for a far shorter period may not be so susceptible to the HWSE and therefore there is no flattening of risk at higher cumulative doses. It is more difficult to see how the HWSE might be the only cause of the observed difference in lung cancer risk between the two sub-cohorts.

If this was true, a reduction in risk among the higher exposed potentially monitored internal radiation workers could be expected and not zero excess risk over the whole dose range.

Clearly smoking is a likely cause of many of the lung cancer cases and therefore variations in the pattern of smoking between the external radiation workers and those also internally monitored could result in differing dose response relationships. However, the pattern of variation in smoking between internal and external radiation workers may be complex. Internal radiation worker in the NRRW cohort may experience more restrictive working environments (e.g., mask wearing) which might mean their opportunities for smoking at work were less than those for external radiation workers. In addition, smoking rules for radiation workers at their place of work will have changed over the decades and may have changed in different ways and at different times between internal and external workers.

Another factor for internal radiation workers is that over a longer employment period they will have had greater occupational health surveillance than the typical external radiation worker and therefore be more often advised about the health impacts of smoking and other lifestyle factors. There also have been a very significant reduction in the proportion of the male population smoking from the 1950s to today.

Studies of the Japanese A-bomb survivors, medically exposed groups, radiation workers in Mayak PA in Russia and have demonstrated increases in lung cancer risk with external radiation dose regardless of whether an adjustment was made for smoking status (23). The joint effects of external radiation and smoking on lung cancer was investigated in the A-bomb study and were consistent with a generalized multiplicative model (GMM) interaction; the risk estimates were greater for light/moderate smokers than that for heavy smokers with little or no apparent radiation effect (13, 24). Another potential factor that may be affecting the lung cancer risks in the NRRW among the internally monitored workers is their unknown internal exposures. When an additional sensitivity analysis was conducted where the baseline risk model was adjusted for internal monitoring status it gave similar results to those from the main analysis of solid cancers or lung cancer and the LE remained statistically significant.

Internal exposures are known to be a risk factor for lung cancer e.g., among Mayak workers exposed to plutonium and among miners and the general population exposed to radon (14, 25–29). The joint effects of radon exposure and smoking among miners and in general population (from residential radon exposure) on lung cancer risk showed a sub-multiplicative interaction; the risk was greater for non-smokers compared with current or ex-smokers, although there was no statistically significant variation in risk estimates by smoking status (25-27). For the Mayak workers, the risk for lung cancer was statistically significantly higher among non-smokers than among smokers in relation to internal plutonium lung doses, suggesting also a sub-multiplicative relationship, although smoking rates in males and females were very different, 74% and 4%, respectively, among individuals with known smoking status (28, 29).

If in this study workers in the highest dose category were longer-term smokers than the low-dose category workers of light smokers then based on what was seen in the A-bomb survivors and other exposed internal exposed population a weak/flat dose response would be expected in these exposed workers in the NRRW cohort and this was the case. A different hypothesis for the lack of dose response relationship between lung cancer among the internally monitored workers here is that their lung cancer risk is more strongly related to their internal lung dose than their external dose. If workers internal and external doses were uncorrelated then this might result in a lack of a dose response with external dose among the internally exposed workers. However, we do not have the internal dose measurements and some of them may not have received any internal dose as their monitoring may have just been precautionary (5). A joint study of lung cancer risk among BNFL-Sellafield and Mayak workers (15) found a much greater excess risk per Gray (Gy) for lung cancer incidence in the Sellafield workers related to their plutonium exposure than their external gamma exposure however direct comparisons with this study are difficult due to issues of plutonium dose estimation in the Sellafield workers (30).

Since smoking is a major cause of many cancers (31, 32), the same group of all smoking related cancers (cancers of the oral cavity, nasal cavity and paranasal sinuses, esophagus, stomach, colon, rectum, liver, gallbladder, pancreas, larynx, lung, female ovarian and uterus, bladder and kidney) as used in INWORKS (3) was examined to see if the effects observed for lung cancer were seen more widely. There was good evidence of an increasing linear trend with dose (ERR/Gy = 0.28, 95% CI: 0.02; 0.57, P = 0.03) and no evidence of non-linearity for all radiation workers. For the external radiation worker sub-cohort that account for 70% of the cases, the evidence remained good and the slope of the dose response increased (ERR/Sv = 0.62, 95% CI: 0.09; 1.23, P = 0.02) but for the internally

monitored radiation worker sub-cohort the evidence of a linear trend with external dose slightly weaker (ERR/Sv = 0.28, 95% CI: –0.007, 0.62, P = 0.056), but with a slope estimate the same as that for all radiation workers and with no evidence of non-linearity (not shown here). Again, The INWORKS study and that of the Japanese radiation workers (3, 18) reported no evidence for a dose-response relationship between smoking related cancer mortality and radiation exposure, although our estimate was consistent to that from INWORKS (ERR/Gy = 0.37, 90% CI: –0.14; 0.95). The result for smoking-related solid cancers incidence from the Japanese A-bomb study (1) was statistically significant, although in that study the excess risk estimate was about half that of our estimate with the ERR of 0.16 at 1 Gy resulted from a LQ trend in males over the dose range 0–2 Gy.

While this study provides good evidence for a linear–dose response for solid cancers excluding lung over the whole dose range and for lung cancer up to among the externally exposed workers the picture is not clear for the internally monitored workers. For these workers it seems likely that the shapes of the dose response relationships are being influenced by at least one or more of the factors described above. Without extra information about internal exposures and about lifestyle factors such as smoking further explanation of the dose response may not be possible however additional follow-up may help.

### *Radiation Effects at Low Doses*

Epidemiological studies on populations exposed to large acute radiation doses, such as the atomic bomb survivors or radiotherapy patients, have shown a significant increase in cancer risk at doses above 100 mSv (33). Risk from exposures below that level remain the subject of considerable scientific debate because the effects at low dose levels have not yet been clearly established in studies of either epidemiology or radiobiology (22). In this study 95% of the workers received a cumulative dose less than 100 mSv. In this range there was good evidence of raised risk for all solid cancers combined (ERR/Sv = 0.98, 95% CI: 0.14; 1.86, P = 0.02). However, the strength of the evidence for a linear trend was much reduced when lung cancer was excluding from solid cancers (ERR/Gy = 0.62, 95% CI: –0.29; 1.59, P = 0.13). Our result from solid cancers supports the findings from the INWORKS (3) and the Japanese A-bomb study (1), which have showed an increased risk for the dose range of 0–100 mSv; the risk estimate from INWORKS was similar (ERR/Sv = 0.81; 90% CI: 0.01; 1.64), but the comparable risk estimate in the A-bomb data was less than half our estimate (ERR/Gy= 0.49, 95% CI: 0.026; 1.01).

### *Site-Specific Cancers*

The risk estimates in this study for site-specific cancers were lower for some or higher than that reported in the recent updated 3rd NRRW analysis (6), albeit the confidence intervals generally overlapped, and the findings were in general similar. Such differences that were observed could be explained by the use of different baseline rate modelling in the earlier paper (based on fully stratified modelling) (6). Among the site-specific risk estimates those for cancer of the colorectal, bladder and pleural were significantly increased with radiation (Fig. 6) for which no detail investigation was carried out in the previous analyses (4–6). However, we did not detect raised risk for other specific solid cancers that can be induced by radiation exposure (34). It is likely that low statistical power probably explains the lack of evidence in this study.

### *Colorectal Cancer*

When rectal and colon cancers are grouped together as colorectal cancer, this study provides evidence of a relationship with increasing cumulative exposure to external dose (ERR/Sv = 0.68, 95% CI: 0.12; 1.37, P = 0.016) based on larger numbers of incident cases (2,752 cases). There was no evidence of non-linearity based on the LE model (P > 0.5). However, when the external doses were restricted to less than 500 mSv (excluding 41 cases), there was no evidence for a linear dose-response for colorectal cancer (P = 0.34) and the estimate was reduced by half (ERR/Sv = 0.35, 95% CI: –0.34, 1.19). This study found no evidence of heterogeneity in the dose response between the sub-cohort of externally exposed workers and that of workers also internally monitored (P = 0.28), the external workers do however have a higher ERR/Sv estimate (ERR/Sv = 1.17 95% CI: 0.14; 2.44, N = 1,981) than workers monitored for internal exposure (ERR/Sv = 0.54 95% CI: –0.02; 1.26, N = 771).

Rectal and colon cancers share some hereditary and dietary risk factors, although there is some evidence of differences in their etiology between rectal and colon cancers (35). These cancers were also analyzed separately here. Having adjusted for the baseline risk [Eq. (1)], there was strong evidence for a linear dose response relationship for rectal (ERR/Sv = 1.20; 95% CI: 0.20; 2.53, P = 0.015) based on 1,120 cases (Fig. 7). The results agree well with previous NRRW studies (4–6). However, much of the evidence in this study for the dose response in rectal cancer arose from a small number of cases (13 cases) among workers with lifetime doses exceeding 600 mSv. When the external doses were restricted to less than 600 mSv, the linear effect was no longer statistically significant (P = 0.19) and the estimate was reduced (ERR/Sv = 0.76, 95% CI: –0.33, 2.19, P = 0.19). For colon cancer, there was some indication of an increased risk from external exposure (ERR/Sv = 0.58 (95% CI: –0.021; 1.35, P = 0.06) based on 1,632 cases after adjusting for attained age, sex, birth year, industrial classification and first employment (Fig. 7). Our recent updated 3rd NRRW reported (6) no evidence for dose-response relationship for large intestine (includes colon and peritoneal cases) cancer incidence (ERR/Sv = 0.42, 95% CI: –0.22; 1.28, P = 0.23),

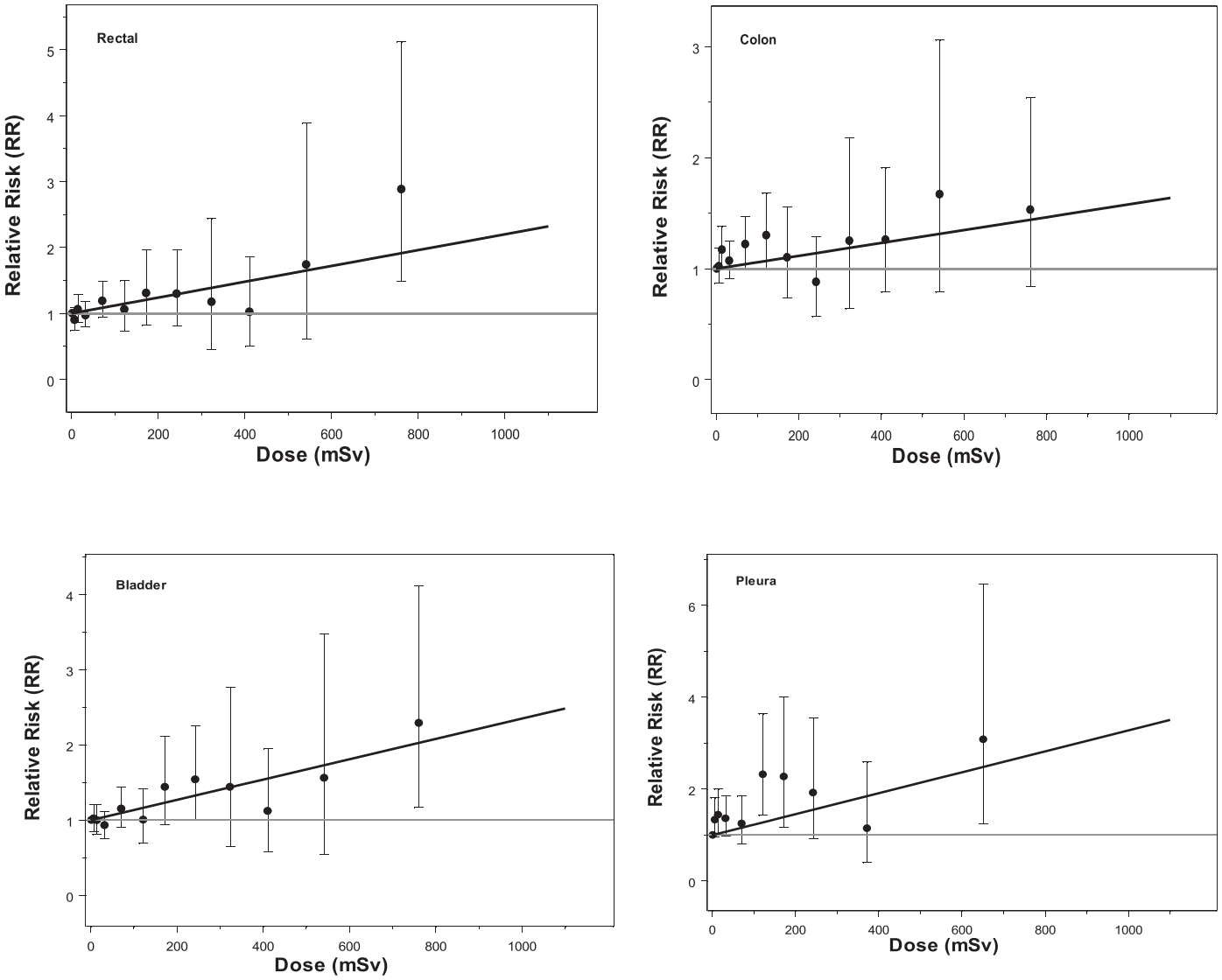


**FIG. 7.** Dose-response function for cancer of rectal and bladder having adjusted for baseline non-radiation factors. The gray horizontal solid line represents a relative risk of 1. (Lagged by 10 years.)

although CI overlap. Analyses here were excluded peritoneal cases. In addition, the original 3rd NRRW analysis using ten years less follow up (4, 5) also found no evidence of a significant association with radiation exposure for large intestine cancer incidence (ERR/Sv=0.026, 95% CI: –0.65; 0.88, N = 899).

While there is a clear association between colon cancer incidence and radiation among the Japanese A-bomb survivors, the corresponding results for survivors for rectal cancer no association found (36). Our estimate for colon cancer risk is statistically compatible with the estimate for A-bomb survivor (35) either based on sex averaged value (ERR/Gy = 0.57, 95% CI: 0.29; 0.89, N = 1,914 cases) or the value for males (ERR/Gy = 0.66, 95% CI: 0.29; 1.16, N = 782). However, our finding for rectal cancer is not consistent with findings for the A-bomb survivors where a lower estimate was reported for sex averaged (ERR/Gy = 0.02, 95% CI: –0.07; 0.10, N = 1,046) based on organ dose to bladder with using new dosimetry (35). The risk estimates obtained here are consistent with the estimates from the mortality data in the INWORKS (37) for rectum (ERR/Gy = 1.87, 90% CI: 0.04; 4.52, N = 539 deaths) and also for colon cancer (ERR/Gy = 0.42, 90% CI: –0.32, 1.13, N = 1,570 deaths). However, other radiation worker studies in Canada (20), Russia (11, 12) and Japan (19) have not reported increased risks of rectal or colon cancer in relation to radiation exposure, but these studies power to detect a risk if it exists is currently low because of the small number of cases. Studies of patients treated with radiation for prostate cancer do show raised risk of rectal cancer, but based on rectal doses of tens in Sv, UNSCEAR concluded that it is difficult to characterize any risk of rectal cancer due to radiation doses below 1 Sv (23). Although the findings at low-dose level for rectal or colon cancer from the current

analysis are based on relatively large number of cases when compared with some other types of cancer, the 95% confidence interval for the ERR/Sv estimate is wide and encompasses the estimated ERR/Sv from this analysis for all solid cancers combined. Lifestyle-related factors such as smoking, alcohol, meat consumption and body mass index (BMI) have been linked with increased risk of colorectal cancer, but this information is currently not available for NRRW radiation workers.

*Bladder Cancer*

There was good evidence of increased risk with increasing radiation exposure for bladder cancer (ERR/Sv = 1.35, 95% CI: 0.35; 2.67, P = 0.005) after adjusting for the baseline risk [Eq. (1)], is also shown in Fig. 7. This risk estimate was larger than the estimate from the original 3rd NRRW incidence analysis (ERR/Sv = 0.65, 95% CI: –0.28; 1.96, P = 0.20), but CIs overlap. The evidence of a trend seen here in comparison with the original NRRW-3 may be the result of additional statistical provided by the increase in cases from 748 cases in the original NRRW to 1,160 in this analysis. The evidence of increasing trend was not statistically significant anymore when the data used were restricted to cohort members under either 200 mSv or 100 mSv (P = 0.11, P = 0.36, respectively). There was no evidence of heterogeneity in the dose response between the sub-cohort of externally exposed workers and that of workers also internally monitored (P > 0.5), the external workers sub-cohort do however have a lower ERR/Sv estimate (ERR/Sv = 1.28 95% CI: –0.32; 3.40, N = 825) than workers monitored for internal exposure (ERR/Sv = 1.37 95% CI: 0.28; 2.87, N = 335). This finding suggest that those workers monitored for internal exposure are driving the radiation effect for the main analysis.

Our findings are consistent with those from the study of the Japanese A-bomb survivors (34), which found statistically significantly elevated risk based on bladder dose amongst males (ERR/Gy = 0.61, 90% CI: 0.11; 1.20). The risk for patients who were exposed to very high bladder doses during radiotherapy was also reported to be positive (22). As in the original 3rd NRRW mortality analyses, the INWORKS (16) also reported no evidence of significant association with radiation for bladder cancer mortality (ERR/Gy = 0.33, 90% CI: –0.63; 1.21, N = 579 deaths), which NRRW data contributed about half of the deaths. Studies of radiation workers in Russia (11, 12), Canada (20) and Japan (19) did not report any association between bladder cancer and radiation exposure; low statistical power due to low numbers of cases may explain the lack of evidence of a radiation related bladder cancer risk in these studies of nuclear workers other than this study. Tobacco smoking is the main risk factor identified for cancer of bladder, which may be partially influencing the association of external exposure with bladder cancer risk in this study. However, information on lifestyle, smoking and occupational chemical exposure are not available in the NRRW data and thus it is not possible to account for them in this analysis.

*Pleural Cancer*

This study found an evidence of a linear-dose-response relationship for pleural cancer with increasing cumulative exposure to radiation exposure (ERR/Sv = 2.28, 95% CI: 0.39; 5.12, P = 0.01, N = 397) after adjusting for attained age, sex, birth cohort, industrial classification and first employer (Fig. 7). The trend estimate was similar to that estimate reported in the recent updated NRRW-3 analysis of incidence. However, the original 3rd NRRW analyses found no statistically significant trend with dose either in incidence of pleural cancer due to the small numbers, 190 cases (4, 5).

The evidence of increasing trend was not statistically significant anymore when the data used were restricted to 0–100 mSv (P = 0.29). There was no evidence of heterogeneity in the dose response between the sub-cohort of externally exposed workers and that of workers also internally monitored (P > 0.50), the external workers do however have a higher ERR/Sv estimate (ERR/Sv = 3.19, 95% CI: 0.11; 7.75, N = 300) than workers monitored for internal exposure (ERR/Sv = 1.85 95% CI: −0.02; 1.26, N = 97).

The U.S. pooled nuclear worker study (38) based on mortality data found no evidence of a trend with dose in pleura cancer and mesothelioma combined (ERR/Sv = 2.5, 95% CI: –1.30; 10.0, N = 99), which is similar to our risk estimate. The INWORKS (36) which included a subset of NRRW and a subset of the U.S. radiation workers also reported no association for the mortality analysis and again the central estimate from INWORKS (ERR/Gy = 2.62, 90% CI: –0.56; 7.37, N = 273 deaths) was similar to our and the U.S. estimate.

The overwhelmingly well-established risk factor for pleural cancer is exposure to asbestos (39). These findings may suggest that exposure to asbestos may be positively correlated with radiation dose within these cohorts. While there is no information in the NRRW on individuals' potential for asbestos exposure, it is highly likely that the increased risk for pleural cancer in this study is due to asbestos rather than radiation exposure. Asbestos was widely used in building industry, shipbuilding and power stations; Among the 397 pleural cases in this present study, the more than half of the cases were from MoD (124 cases), 90 cases from BNFL and 61 cases from England and Wales nuclear power stations. Excess deaths from pleural cancer were observed at the U.S. Navy nuclear shipyard (38) and it is likely that UK shipyard workers had similar exposure experiences (40). Needs more detail on work history information for those workers with pleural cancer e.g., asbestos exposure and where they worked.

## SUPPLEMENTARY INFORMATION

Supplementary Table S1. Study population by year of birth, lifetime dose and gender (female numbers are in parenthesis) based on unlagged data.

Supplementary Table S2. The interaction effect between radiation and various temporal factors of interest for solid cancer excluding lung cancer (lagged by 10 years).

Supplementary Table S3. Relative risk (RR), ERR/Sv with 95% confidence intervals (CI) for individual solid cancer sites based on 10-year lag-period with adjustment for baseline rates.

## ACKNOWLEDGMENTS

The authors thank all the organizations and individuals participating in the NRRW for their cooperation and support. We also thank the many current and past PHE/HPA/NRPB staff who have assisted the NRRW. We wish to acknowledge the help of Mary Phillipson and Tina Wilcock for data management support throughout the course of project. Key people Colin Muirhead and Gerry Kendall in developing the database and valuable advice over many years and Jackie O'Hagan for database management. The findings and conclusions are those of the authors and do not necessarily represent the views of Public Health England. We would also like to thank all reviewers for their comments that helped us greatly improve the manuscript.

Received: December 2, 2020; accepted: April 1, 2022; published online: April 22, 2022

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