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Mortality from Circulatory Diseases and other Non-Cancer Outcomes among Nuclear Workers in France, the United Kingdom and the United States (INWORKS)

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Abstract

Positive associations between external radiation dose and non-cancer mortality have been found in a number of published studies, primarily of populations exposed to high-dose, high-dose-rate ionizing radiation. The goal of this study was to determine whether external radiation dose was associated with non-cancer mortality in a large pooled cohort of nuclear workers exposed to low-dose radiation accumulated at low dose rates. The cohort comprised 308,297 workers from France, United Kingdom and United States. The average cumulative equivalent dose at a tissue depth of 10 mm [Hp(10)] was 25.2 mSv. In total, 22% of the cohort were deceased by the end of follow-up, with 46,029 deaths attributed to non-cancer outcomes, including 27,848 deaths attributed to circulatory diseases. Poisson regression was used to investigate the relationship between cumulative radiation dose and non-cancer mortality rates. A statistically significant association between radiation dose and all non-cancer causes of death was observed [excess relative risk per sievert (ERR/Sv) = 0.19; 90% CI: 0.07, 0.30]. This was largely driven by the association between radiation dose and mortality due to circulatory diseases (ERR/Sv = 0.22; 90% CI: 0.08, 0.37), with

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slightly smaller positive, but nonsignificant, point estimates for mortality due to nonmalignant respiratory disease (ERR/Sv = 0.13; 90% CI: −0.17, 0.47) and digestive disease (ERR/Sv = 0.11; 90% CI: −0.36, 0.69). The point estimate for the association between radiation dose and deaths due to external causes of death was nonsignificantly negative (ERR = −0.12; 90% CI: <−0.60, 0.45). Within circulatory disease subtypes, associations with dose were observed for mortality due to cerebrovascular disease (ERR/Sv = 0.50; 90% CI: 0.12, 0.94) and mortality due to ischemic heart disease (ERR/Sv = 0.18; 90% CI: 0.004, 0.36). The estimates of associations between radiation dose and non-cancer mortality are generally consistent with those observed in atomic bomb survivor studies. The findings of this study could be interpreted as providing further evidence that non-cancer disease risks may be increased by external radiation exposure, particularly for ischemic heart disease and cerebrovascular disease. However, heterogeneity in the estimated ERR/Sv was observed, which warrants further investigation. Further follow-up of these cohorts, with the inclusion of internal exposure information and other potential confounders associated with lifestyle factors, may prove informative, as will further work on elucidating the biological mechanisms that might cause these non-cancer effects at low doses.

INTRODUCTION

It has long been established that exposure to ionizing radiation increases the risk of cancer (1–3), and can also cause non-cancer disease, as in acute high-dose exposure scenarios resulting in immediate tissue damage (3). There is documented evidence of a dose-related excess risk of circulatory disease in Japanese atomic bomb survivors (4–7). At higher, yet still moderate dose rates, studies of patients treated by radiotherapy of the left breast also demonstrate clear evidence of subsequent cardiovascular disease mortality risk several years postirradiation (8–12). Circulatory disease is not the only non-cancer disease that may be a late effect of radiation exposure. For example, recently reported evidence also suggests a dose-related excess risk of mortality due to digestive and respiratory diseases among Japanese A-bomb survivors (7).

Although the Life Span Study (LSS) of Japanese A-bomb survivors and epidemiological studies of patients externally exposed to ionizing radiation at high dose rates for radiotherapeutic purposes, are valuable sources of information about radiation risks, such studies do not directly address questions regarding disease risks associated with the protracted or intermittent low-dose-rate exposures typically encountered by workers and the general public. Consequently, the effects of lower doses of radiation, and of protracted exposures to both external and internal ionizing radiation, on non-cancer outcomes are far less clear. However, there is growing evidence that low-to-moderate doses of ionizing radiation may increase the risk of some non-cancer diseases with evidence of excess disease appearing after a relatively long interval postirradiation (3, 13–16).

In the current study, associations between low-level exposure to ionizing radiation and non-cancer disease mortality were examined among nuclear industry workers from France, United Kingdom (UK) and United States (U.S.), as part of the International Nuclear Workers Study (INWORKS). This study is an extension of an international study of workers in three countries (17), which was first established in the 1990s and then later extended to include 15

countries (18). The worker cohorts from France, UK and U.S. provided the vast majority of information on early nuclear workers in that study (18), and information from these three cohorts has been updated since that 15-country study (19–21). Here, we report on our analysis of non-cancer mortality with an emphasis on circulatory disease mortality. Analyses of deaths due to malignant disease have been reported previously (22–24).

METHODS

The methods used in this analysis are similar to those used in previous analyses of these combined pooled cohorts (22–26); for the sake of completeness, these methods are summarized below.

Study Design and Participants

The study population was defined as nuclear industry workers from France, UK and U.S. who were employed in at least one of the study facilities for at least one year and who had dosimetry records indicating that they were monitored for external radiation exposure. Data for French workers were obtained from three major employers: Commissariat à l'Energie Atomique (CEA), AREVA Nuclear Cycle (AREVA) and Electricité de France (EDF) (19). Data for UK workers were obtained from the National Registry for Radiation Workers (NRRW), which contains information provided by the Atomic Weapons Establishment (AWE), British Nuclear Fuels Ltd. (BNFL), the United Kingdom Atomic Energy Authority (UKAEA), British Energy Generation and Magnox Electric (BEGME) and the UK Ministry of Defence (MOD) (20). Data for U.S. workers were obtained from the Department of Energy's Hanford Site, Savannah River Site (SRS), Oak Ridge National Laboratory (ORNL) and Idaho National Laboratory (INL), as well as from Portsmouth Naval Shipyard (PNS) (21).

Dosimetry Data

For each worker, individual annual recorded radiation doses were obtained from facility records and/or national dose registries. Bias and uncertainty in recorded doses vary among facilities and across time as a result of differences in dosimeter response to photon energies, exposure geometry, dosimeter type and dosimetry methods. These sources of measurement uncertainty were examined by facility and time to derive bias factors for normalizing exposures to a measurement of worker dose (25). Dose was expressed in sievert (Sv) and defined as equivalent dose at a tissue depth of 10 mm, which is consistent with the operational quantity for penetrating radiations [Hp(10)] (25). In this article, Hp(10) doses have been used for the analysis of all non-cancer outcomes. Neutron exposures were expressed as a time-varying indicator variable for each worker, classifying them according to whether they had a positive recorded neutron dose that ever exceeded 10% of their total external penetrating radiation dose.

Information about incorporated radionuclides varied and included bioassay results, indication of confirmed uptake (e.g., fraction of a body burden or annual limit on intake), or an assigned committed dose, although for the majority of workers monitored for internal radiation, only the fact that they were monitored was available. For analysis purposes, we

grouped these measurements as an indication of a known or suspected internal contamination. French and U.S. workers with a known or suspected uptake were identified, as were UK workers who were known to have been monitored for internal exposure.

Follow-up and Ascertainment of Causes of Death

The French, UK and U.S. cohorts were followed to ascertain vital status through to 2004, 2001 and 2005, respectively. A person entered the study at either the date of first monitoring or one year after start of employment at one of the included facilities, whichever was the latter. The French cohort was followed from 1968 at the earliest, due to the lack of individual causes of death in national registries before then. Workers exited the study at the earliest date of any of the following events: death, loss to follow-up or end of follow-up.

Vital status was determined through linkage with national or regional death registries. Information on underlying cause of death was obtained from death certificates and coded according to the appropriate revision of the International Classification of Diseases (ICD). Results are presented for mortality from all non-cancer diseases combined (ICD9: 1–139, 240–E999 except 273.3) and for 12 groupings of specific non-cancer diseases, including circulatory diseases (ICD9: 390–459), respiratory diseases (ICD9: 460–519), digestive diseases (ICD9: 008–009, 520–579) and external causes of injury, poisoning and adverse effects (ICD9: E800–E999). A full tabulation of the specific non-cancer diseases considered in this study is given in Supplementary Table S1 (http://dx.doi.org/10.1667/RR14608.1.S1) along with associated ICD codes that have been used in creating these groupings. Particular attention is paid to circulatory diseases, because of the evidence from previous studies discussed above, and to the main subtypes of circulatory disease: ischemic heart disease (IHD, ICD9: 410–414) and cerebrovascular disease (ICD9: 430–438). Only underlying causes of death were used in the analysis.

Statistical Methods

The objective of the statistical analysis was to assess how the rate of mortality from non-cancer outcomes changes in relationship to cumulative doses from external exposure to penetrating photons, taking into account available information on potential confounding factors such as gender, attained age, birth cohort, socioeconomic status, duration of employment, employer/facility of employment and exposure to other forms of radiation. Poisson regression models were used to estimate the relative rate of death for non-cancer diseases as a function of cumulative external radiation dose. The models considered were of the following form:

$$\lambda(a,b,g,f,s,l,d)=\lambda_0(a,b,g,f,s,l)[1+\mathrm{ERR}\,(d)],$$

where a is the attained age, b is birth cohort, g is the gender, f is facility of employment, s is the socioeconomic status, l is duration of employment, ERR is the estimated excess relative risk and d is the cumulative external photon dose.

To perform the analysis, the data were organized in a multidimensional person-years table. The data in this tabulation were distributed into categories for each of the risk factors and

time-dependent lagged cumulative external radiation dose; the number of person-years accumulated and the death count were included in each cell.

Fully parametric, semiparametric and stratified models were considered for the baseline hazard function λ_0, but produced broadly similar results. The results are shown using a model containing stratified adjustment for age, birth-cohort, gender, employer/facility and main effect adjustments for the socioeconomic status and duration of employment that varied by country. For the main analyses, the relative rate was quantified as a linear function of cumulative dose, where $\mathrm{ERR}(d) = \beta d$. To allow for an induction and latency period between exposure and death and to enable comparison with previously published study results (18–22), cumulative dose was lagged by 10 years in the main analysis. Although most of the ERR estimates presented here are based on a linear ERR model [$\mathrm{ERR}(d) = \beta d$], the linearity of the ERR estimates was also tested by comparing the relative fit of the linear model to linear quadratic [$\mathrm{ERR}(d) = \beta_1 d + \beta_2 d^2$], quadratic [$\mathrm{ERR}(d) = \beta d^2$] and linear exponential [$\mathrm{ERR}(d) = \beta_1 d \exp(\beta_2 d)$] models.

As is common with other major radiation worker studies we have used the “fixed effect” assumption in this analysis, i.e., we have assumed that the radiation effect (if there is one) is fixed and equal across all of the population groups used in this study. In addition, analyses were performed to evaluate employer/facility of employment, gender, socioeconomic status, duration of employment and attained age as potential effect modifiers. To address concerns about potential residual confounding, many of the detailed analyses (including the dose-response analysis) were restricted to the 98.2% (302,507 workers) of workers with known socioeconomic status and detailed individual monitoring data for external exposure to ionizing radiation that could be attributed to main employer/facility groups included in the analysis cohort (i.e., excluding those of unknown employer/facility of employment or uncertain socioeconomic status). Further sensitivity analyses were adjusted for the potential effect of occupational exposures to neutron and internal exposures.

Temporal variation in the effect of exposure was examined through the analysis of age-at-exposure and time-since-exposure windows. Defined windows were used to evaluate variation in risk by age-at-exposure (<35, 35–50 and ≥50 years) and time-since-exposure (10–20, 20–30 and ≥30 years). For age-at-exposure and time-since-exposure, the cumulative doses received in each of the three categories were modeled jointly with each window categorized into the same set of dose categories used in the main lagged analysis (defined in Supplementary Table S2; http://dx.doi.org/10.1667/RR14608.1.S1), and the likelihood of this model was tested against that of the standard model with 10-year lagged total cumulative dose. As with previous country-specific analyses of non-cancer outcomes in these cohorts, the main analysis is based on 10-year lagged doses, however, results for alternative lagging periods of 0, 2, 5, 15 and 20 years were also considered in the supplementary analyses.

Parameter estimates were computed using maximum likelihood methods. Hypothesis tests and confidence intervals were based on likelihood ratio tests and direct evaluation of the profile likelihood. We have reported 90% confidence intervals (90% CI) for the ERR parameter estimates to be consistent with previously reported studies. Therefore, the results

may be interpreted as a one-sided test at the 5% level of statistical significance. All analyses were performed using the AMFIT module of EPICURE software (27). Due to computational constraints, only disease groups with more than 100 deaths have been examined in the main analysis. Because the main interest in this study was circulatory diseases, the full range of sensitivity analyses are shown only for these diseases and their main subgroups: IHD and cerebrovascular disease. Supplementary Table S2 (http://dx.doi.org/10.1667/RR14608.1.S1) contains further details of the definition of the variables used either in the main or sensitivity analysis.

RESULTS

The study population for this analysis consisted of 308,297 workers (Table 1). A total of 66,632 (22%) people were known to be deceased at the end of follow-up. Of these deaths, 46,029 (69%) were due to non-cancer causes, the majority of which [27,848 (60%)] were due to circulatory diseases. Overall, the follow-up of this pooled cohort encompassed 8.2 million person-years and an accrued collective dose of 7,772 person-Sv. The average cumulative dose was 25.2 mSv, but dose distribution was very skewed with a median dose of 3.4 mSv, a 90th percentile dose of 64.5 mSv and a maximum dose of 1,932 mSv. Most workers were exposed to relatively low levels of radiation, with 203,368 (66%) workers receiving less than 10 mSv cumulative dose. However, the pooled cohort also included a significant number of workers with moderate-to-high cumulative occupational exposures. There were 19,697 (6.4%) workers accruing doses of more than 100 mSv, 2105 (0.7%) more than 400 mSv and 83 workers above 1 Sv from exposures over their working lifetime.

Disease-specific non-cancer mortality ERR/Sv estimates are shown with respect to cumulative external dose lagged 10 years for the INWORKS cohort (Table 2). For all non-cancer diseases, a statistically significant ERR/Sv = 0.19 (90% CI: 0.07, 0.30) was found (Table 2), which was largely driven by circulatory diseases (ERR/Sv = 0.22; 90% CI: 0.08, 0.37). Among other major causes, elevated but nonsignificant ERR/Sv point estimates were also observed for respiratory disease [ERR/Sv = 0.13; 90% CI: −0.17, 0.47 (5,291 deaths)] and digestive diseases [ERR/Sv = 0.11; 90% CI: −0.36, 0.69 (2,180 deaths)]. The point estimate of ERR/Sv for external causes, which accounted for 4,451 deaths, was nonsignificantly negative and highly imprecise (ERR/Sv = −0.12; 90% CI: <−0.60, 0.45). Among other causes, only mental disorders showed a significantly elevated linear ERR/Sv estimate [ERR/Sv = 1.30; 90% CI: 0.23, 2.72 (based on 705 deaths)].

More than half of circulatory disease deaths were due to IHD and a significantly elevated ERR/Sv was observed for IHD [(ERR/Sv = 0.18; 90% CI: 0.004, 0.36 (based on 17,463 deaths)]. The vast majority of IHD deaths were attributed to acute myocardial infarction (MI) or chronic IHD, and the overall IHD ERR/Sv estimate was largely driven by acute MI [ERR/Sv = 0.26; 90% CI: 0.03, 0.51 (based on 11,076 deaths)] with little evidence of raised risk for chronic IHD [ERR/Sv = 0.07; 90% CI: −0.19, 0.36 (based on 6,238 deaths)], although there was little evidence of heterogeneity in risk between these main subtypes of IHD ($P = 0.38$). The ERR/Sv estimate for other heart diseases (non-IHD), which accounted for 3,398 deaths, was not materially different from that of IHD.

Cerebrovascular diseases, which accounted for 4,444 deaths, also showed a significantly raised ERR/Sv (ERR/Sv = 0.50; 90% CI: 0.12, 0.94), which is somewhat higher than that observed for IHD, although not significantly so ($P = 0.21$). No differences in ERR/Sv were apparent in the cerebrovascular disease subgroups, although the majority of deaths (61%) were coded to ill-defined cerebrovascular diseases, perhaps reflecting the accuracy of specific coding within this subgroup. Further details on the ERR/Sv estimates for the main subtypes of circulatory disease are available in Supplementary Table S3 (http://dx.doi.org/10.1667/RR14608.1.S1).

Since smoking is a recognized cause of both IHD and cerebrovascular diseases it is possible that the observed positive associations of these diseases with radiation exposure are confounded by smoking. To address this issue, we estimated the excess risk for deaths attributed to chronic obstructive pulmonary disease (COPD), which is much more strongly associated with smoking than IHD or cerebrovascular disease, and found the ERR/Sv to be nonsignificantly negative (ERR/Sv = −0.07; 90% CI: −0.45, 0.38) based on 2,771 deaths (Supplementary Table S4).

Shape of the Dose Response

The shape of the dose response for circulatory diseases, IHD and cerebrovascular diseases was examined by comparing the dose category-specific ERR estimates with the ERR/Sv estimate from the linear model (Fig. 1 and Supplementary Table S5; http://dx.doi.org/10.1667/RR14608.1.S1). Similar results for respiratory and digestive diseases (Supplementary Figs. S1 and S2) showed little evidence for a trend in risk with dose.

For circulatory diseases, the categorical model (Fig. 1A) suggested a linear model adequately approximated the dose-response function. This was confirmed by fitting alternative, quadratic, linear quadratic and linear exponential models that did not markedly improve model fit ($P > 0.50$). The association between radiation dose and IHD was also best described by a linear model ($P > 0.50$), although the 90% confidence interval did not exclude 0 when analyses were restricted to doses below 300 mSv (Fig. 1B). The pattern for cerebrovascular disease was slightly different, with some evidence that the ERR was better described by linear exponential model than a linear model ($P = 0.017$), with increased risks at lower doses and a flattening of risk at doses above 200 mSv (Fig. 1C).

We estimated the ERR/Sv after restricting the analysis by excluding deaths and person-years of experience above a specified dose level (Table 3). For circulatory diseases as a whole, the 90% confidence interval for the association between dose and mortality excluded 0 when estimated over the range of 0–300 mSv; point estimates obtained in analyses restricted over lower dose ranges remain relatively close to estimates obtained over the full dose range, even down to the range of 0–100 mSv (ERR/Sv = 0.14; 90% CI: −0.45, 0.76). For IHD, significant associations were detectable down to 500 mSv. A different pattern was observed for cerebrovascular disease with ERR/Sv estimates increasing when dose range was decreased.

Variation in ERR between Country and Employer/Facility

There was significant variation in the ERR/Sv for circulatory disease by employer/facility (P = 0.01) (Fig. 2 and Supplementary Table S6; http://dx.doi.org/10.1667/RR14608.1.S1). Analyses excluding a single employer/facility at a time revealed four employer/facilities, which when individually excluded, resulted in a relative change in the absolute value of the pooled estimate that was greater than 10%. These were Sellafield/Chapelcross (−73%, ERR/Sv = 0.06; 90% CI: −0.11, 0.24), UKAEA (+23%, ERR/Sv = 0.27; 90% CI: 0.12, 0.44), PNS (+18%, ERR/Sv = 0.26; 90% CI: 0.11, 0.41) and INL (+13.6%, ERR/Sv = 0.25; 90% CI: 0.10, 0.40). However, the combined effects of excluding these four facilities together canceled each other out, resulting in a pooled estimate in the reduced cohort (ERR/Sv = 0.27; 90% CI: 0.05, 0.50) that appeared in good agreement with that of the full cohort and there was no longer evidence of heterogeneity in risk among facilities (P > 0.50).

For IHD the evidence for differences in ERR/Sv among countries (P = 0.09) or facilities (P = 0.18) was somewhat weaker, although differences persisted with significantly raised risks observed in some UK facilities and a significantly negative risk observed in a U.S. facility (Supplementary Table S6; http://dx.doi.org/10.1667/ RR14608.1.S1). For cerebrovascular disease, there was no evidence of a difference in ERR/Sv among countries (P > 0.50) and facilities (P = 0.14) and the UK and U.S. ERR/Sv estimates were virtually identical (UK: ERR/Sv = 0.51; 90% CI: 0.04, 1.07 and U.S.: ERR/Sv = 0.52; 90% CI: −0.09, 1.22).

Differences in ERR in Relationship to Age, Gender, Duration of Employment and Socioeconomic Group

The average cumulative dose among the females was very low (4.9 mSv), and there was little information at higher doses (seven circulatory disease deaths above 200 mSv); however, there was significant evidence of differences in circulatory disease ERR/Sv estimates between males and females (P = 0.005), with females having a higher ERR/Sv than males for both IHD and cerebrovascular diseases, although the uncertainty on their estimate was large (Table 4). Further details on the female circulatory risks by cumulative dose category and the associated shape of the dose response are shown in Supplementary Table S7 and Fig. S3 (http://dx.doi.org/10.1667/RR14608.1.S1).

There was no statistically significant variation in ERR/Sv estimates with attained age (Table 4) for either circulatory diseases (P = 0.21), IHD (P = 0.17) or cerebrovascular diseases (P = 0.33). There was also no evidence of variation in the ERR/Sv by duration of employment (P > 0.50).

For circulatory diseases as a whole, there was no evidence that ERR/Sv was modified by socioeconomic grouping (P = 0.18), however, within the subtypes of circulatory disease, different risk patterns were observed for IHD and cerebrovascular disease. For IHD, white-collar workers (professional, technical, administrative staff and nonindustrial workers) were found to have a significantly higher ERR/Sv (ERR/Sv = 0.58; 90% CI: 0.22, 0.98) than blue-collar workers (ERR/Sv = 0.07; 90% CI: −0.11, 0.27). The opposite pattern was observed for cerebrovascular diseases, although nonsignificantly (P = 0.20), with higher risks observed among the blue-collar workers (ERR/Sv = 0.59; 90% CI: 0.18, 1.07).

Temporal Variation in ERR

There was no evidence of a difference in radiation-related risk of circulatory diseases (IHD or cerebrovascular diseases) by age at which dose was received, although there was a general pattern for the point estimate of ERR/Sv associated with the dose received before age 50 to be higher than the ERR/Sv associated with doses received at older ages for IHD (Table 5).

When considering alternative lagging strategies, estimates tended to increase with increasing lag assumptions for circulatory diseases, IHD and cerebrovascular diseases; however, slight differences were evident between the pattern of IHD and cerebrovascular disease ERR/Sv estimates, with ERR/Sv declining at the 20-year lag for IHD but continuing to increase for cerebrovascular diseases. This pattern is consistent with the results of the time since exposure analysis, which suggests that doses received many years previously may play a more important role in cerebrovascular disease compared to IHD, although these differences are minor and such a pattern could just as well be explained by chance.

Further Sensitivity Analysis

Although external photons were by far the largest contributor to occupational radiation exposure in the INWORKS cohort, a number of workers in that cohort were exposed to other forms of radiation, namely neutron and internal exposures (mainly uranium, plutonium or tritium).

When the background model was additionally adjusted for internal monitoring status (Table 6), the circulatory disease risk estimate increased slightly (ERR/Sv = 0.27; 90% CI: 0.07, 0.37), but no significant heterogeneity in risk was observed between the workers monitored and not monitored for internal exposure ($P = 0.09$). A similar pattern was observed for IHD and cerebrovascular disease, with the ERR/Sv estimates slightly higher for workers monitored for internal contamination.

When assessing the effect of neutron exposure on risk estimates (Table 6), we excluded workers with a significant recorded neutron exposure (>10% of the total external penetrating radiation dose) from the cohort and found the circulatory disease risks to be virtually unchanged (ERR/Sv = 0.21; 90% CI: 0.07, 0.37). This was not surprising, given that 96% of the cohort were not identified as having significant neutron exposure. The circulatory disease ERR/Sv estimate for 4% of workers with significant neutron exposure had a relatively wide confidence interval (ERR/Sv = 0.51; 90% CI: −0.12, 1.30) and was not statistically different to that for the workers with no significant neutron exposure. Additional analyses using this neutron exposure variable (two levels: no evidence of significant neutron dose and recorded neutron dose >10% of the total external penetrating radiation dose) had little impact on risk estimates, with the risk for circulatory disease (ERR/Sv) increasing from 0.22 to 0.23 per Sv. Again, this result is not surprising, since even among the 13% of workers with a positive monitored neutron exposure this only contributed 4.1% of their total external dose.

DISCUSSION

Pooling worker cohorts provides increased statistical power to investigate the effects of low-dose, low-dose-rate radiation. INWORKS is comprised of nuclear workers from France, UK and U.S. It is one of the most informative cohorts in the world, with men and women who have been monitored for external radiation exposure and who have been followed-up over decades to collect information on causes of death.

In the INWORKS cohort we observed a significant association between all non-cancer mortality and increasing levels of external radiation. This excess risk was largely driven by a significant linear ERR/Sv estimate for circulatory diseases, which in turn was driven by significant risks for the main subtypes of circulatory disease: IHD and cerebrovascular disease. For the other major causes of death within the cohort, nonsignificantly positive-radiation-mortality associations were observed for respiratory and digestive diseases, while a negative-radiation-mortality association was observed for external causes of death that were not statistically significant.

Among the other causes of death examined, the only significantly raised risk was for mental disorders ($P = 0.02$). This association has not been reported previously; therefore, it may well be spurious. That said, 53% of the deaths in this disease grouping are attributed to dementia, and there have been some equivocal suggestions in recent studies of a possible link between Alzheimer's disease and ionizing radiation (28–31). Dementia is an increasingly common cause of death among the elderly, and with extended follow-up these cohorts may provide useful empirical information on any potential effect at low dose.

One of the motivations behind this study was the need for radiation risk estimates with greater statistical power than was available in the 15-country study (32). These risk estimates were derived using extended follow-up information from France, UK and U.S. cohorts. It is clear when the risks derived for this study are compared with the 15-country study results (Table 7), the ability to detect associations is markedly improved. The total number of circulatory disease deaths has more than tripled (from 8,412 to 27,570), due in part to the increased age of the cohorts and the decision to exclude as few workers as possible from this analysis (thus, workers potentially exposed to neutrons or internal contamination were included in this study). The number of workers contributing information at higher doses has substantially increased. In the 15-country study there were 376 circulatory disease deaths above 100 mSv and only six circulatory disease deaths above 500 mSv, while in the current analysis, these numbers increased to 2,799 and 222 deaths, respectively. These gains in statistical power have markedly improved estimate precision compared to the 15-country study.

The central estimates of ERR/Sv obtained in this study are consistent with the latest estimates derived from the LSS of Japanese A-bomb survivors (6, 7) and with risk estimates derived using the latest published LSS dataset (Table 7). In both studies, significant associations were observed for circulatory disease and the subtypes of heart disease and cerebrovascular disease, although the risks per Sv for cerebrovascular disease based on INWORKS is somewhat higher than that derived using the LSS cohort. The central

estimates for respiratory and digestive diseases in INWORKS are very similar in magnitude to those found in the LSS cohort, although much less precise.

There is some debate about generalizing radiation risk estimates based on the LSS cohort to other populations and other exposure settings. The LSS cohort members had a single acute exposure, unlike the nuclear workers who had protracted chronic low-dose-rate exposures. There is also the issue that some of the background risk factors for Western populations are different, partly due to a diet higher in fat, compared to the Japanese LSS population (33), which results in higher rates of cardiovascular disease in the INWORKS population. A possible exception is cerebrovascular disease, which is a much more common cause of death in the LSS cohort, accounting for 50% of circulatory disease deaths compared to only 16% in the INWORKS cohort. Also, the age of the two cohorts is very different: 65% of LSS cohort members have died compared to 21% of INWORKS cohort members. The current study shows some evidence of late-onset cerebrovascular disease from radiation exposure; therefore, the ERR/Sv estimate for this cause of death may change with extended follow-up.

In published studies of the Russian Federation Mayak nuclear workers, associations between external radiation exposure and circulatory disease have also been reported (34), with significant effects noted for IHD mortality and morbidity (35) and cerebrovascular disease morbidity (36–37). Mayak relative risk per unit dose estimates were similar to our estimates for circulatory disease mortality and IHD mortality; however, there was little evidence of increased risks of cerebrovascular disease mortality associated with external dose in the Mayak cohort, a significant association only being noted for morbidity.

Both the LSS (single acute exposure, mean dose 0.1 Sv) and Mayak workers (chronic exposure with a mean dose of 0.62 Sv) have exposures that are very different from INWORKS cohort members, who generally had chronic low-dose exposures over a working lifetime with a mean dose of 0.025 Sv. Associations between circulatory disease and external radiation exposure have also been found in other cohorts, most notably among Chernobyl clean-up workers (38) and residents living near the Techa River (39) who were exposed to radioactive discharges from the Mayak plant. In the Chernobyl clean-up worker cohort (mean dose 0.109 Sv), significant associations of a similar magnitude to those observed in this study were noted for circulatory disease outcomes, including IHD and cerebrovascular diseases, although dose estimates in that study are very uncertain. In the Techa River cohort (mean dose 0.035 Sv), a significant association for circulatory disease mortality was driven by a significant association for IHD.

The findings of the current study could perhaps be interpreted as providing reasonably strong evidence to support the above findings of an association between non-cancer effects and radiation exposure, although there are certain heterogeneities in the observed patterns of ERR/Sv that warrant further investigation. For example, there is significant heterogeneity in ERR/Sv among facilities in the study with some cohorts showing some evidence of substantial positive radiation risk estimates for circulatory disease (mainly in the UK) while others show substantially negative radiation risk estimates (mainly in the U.S.).

A possible explanation for negative bias is a selection effect where workers are, based on health status, selected out of continued radiation work and therefore the continued accrual of dose. Given the high prevalence of circulatory disease incidence and the potential for different health monitoring practices, including the response to the manifestation of disease in a worker, it is entirely possible that such a negative bias could be observed in some facilities and not others.

In the 15-country study that preceded this study, attempts were made to eliminate potential sources of bias related to exposure measurement error by excluding workers with internal and neutron exposure from the analysis (17). The current study included such workers and performed sensitivity analyses to determine the likely effect of this approach.

For circulatory diseases, IHD and cerebrovascular diseases, ERR/Sv estimates among workers monitored for internal contamination were observed to be higher than for those who were not monitored; this finding could be the result of a failure to take into account internal exposures. Therefore, interpretation of these results needs to be treated with caution, given the limitations of the internal monitoring information available for analysis.

For most internally monitored workers in this analysis, no information was available about when they were monitored for internal exposure, only that they were monitored at some point. As a consequence, in the analysis, the internal monitoring variable was treated as being fixed from the start of follow-up, i.e., it was assumed that internal monitoring/exposure started at the beginning of follow-up for such workers. In reality, for a large number of workers, a need for bioassay monitoring may have begun many years after starting other radiation work (e.g., in a job/location where there was no potential for internal exposure). This analysis assumption could potentially lead to the issue of “immortal” person-years occurring in the internally monitored subgroup (because of the lack of information about the start date of internal exposure, workers will potentially be contributing person-time into the internally monitored subgroup when, in fact, they are not at risk in that subgroup). This may well have the impact of deflating the rate of disease (deaths/person-years) in the internal subgroup and increasing the rate of disease in the unmonitored subgroup. Since we are dealing with cumulative doses, this process will not be independent of dose level, as the “immortal” years would preferentially be accrued at lower doses (i.e., before the workers were internally monitored). This has the potential impact of inflating the ERR estimate in the internally monitored subgroup and deflating the ERR/Sv estimate in the unmonitored subgroup of workers, and this is the pattern of results observed in the INWORKS cohort.

In recent analyses of the BNFL cohort (an influential component of the UK contribution to the INWORKS cohort), which had additional information on the exact dates of internal exposure, it was notable that the ERR/Sv estimate for internally monitored workers was actually lower than for workers not monitored for internal radiation (40, 41). It may also be possible that internal exposures influence the pattern of risks we are observing; recent findings in the Mayak cohort suggest a possible link between IHD, cerebrovascular disease and plutonium exposure (34–36). However, internal exposures in the Mayak cohort are considerably larger than those in other cohorts. The evidence for an association between

circulatory disease and internal exposure in other cohorts is limited by low power and the evidence for such an effect remains equivocal (42–43).

Tissue dose from internal exposures depend on the biokinetics of the contaminant and higher doses are normally observed in specific organs. For example, for plutonium the main sites of deposition would be the lung, liver and bone with very little exposure to organs such as the heart (44). Thus, the choice of target organ for the analysis will influence the likely contribution of internal exposures to a worker's total radiation dose, but there is no consensus on the most appropriate target organ for use in the analysis of circulatory diseases.

The highest risks observed in the INWORKS cohorts are in facilities that contain the highest proportion of internally monitored workers. For example, in the two cohorts with the highest ERR/Sv estimates of risk for circulatory disease, BNFL (excluding Sellafield/Chapelcross) and AWE (Supplementary Table S6; http://dx.doi.org/10.1667/RR14608.1. S1), the proportion of workers monitored for internal exposure is high (57 and 64%, respectively), and the average external exposures at these cohorts are relatively low (20.2 mSv and 8.6 mSv, respectively), suggesting that internal exposures may account for a substantial proportion of a worker's total occupational radiation dose, depending on the choice of target organ used in the analysis. The failure to take account of internal exposures could therefore potentially influence the ERR/Sv estimate obtained for these cohorts.

The final models selected for estimating risks in this analysis did not include an internal monitoring adjustment, although for completeness, risk estimates using this adjustment have been included in Table 6. Additional information on internal exposure levels and on exact dates of internal monitoring will be useful in future analyses.

Another source of possible bias in the analysis results is the potential effect of both measured and unmeasured neutron doses on risk estimates. Adjustment for measured neutron exposure through the use of the neutron exposure variable had little impact on risk estimates for circulatory disease. However, this result is not surprising, given that even among 13% of the workers with a reported positive monitored neutron exposure, their neutron exposure only contributed 4.1% of their total external dose. Therefore, the overall effect of neutron exposures on risk estimates is likely to be small.

Measurements from early neutron dosimeters were relatively poor compared to data from contemporary devices (45). Furthermore, sources of neutrons and monitoring practices varied widely among facilities over time. Thus, neutron exposure data are likely to be incomplete and significant exposure misclassification is unavoidable in this study. Additional research is needed to elucidate the effects of neutrons in this study and in other studies of populations exposed to mixed radiation fields.

Another limitation of this study, common to most occupational studies, is the absence of information on potential confounders that are known to be risk factors for non-cancer outcomes and particularly circulatory disease. Circulatory diseases have a number of known risk factors, including smoking, diabetes, obesity, hypertension and high levels of blood low-density lipoprotein (LDL) (7). As discussed in the cancer analysis (23) there is, however,

little evidence that the results are confounded by smoking. The ERR/Sv estimate for COPD, a disease strongly associated with smoking, was also found to be nonsignificantly negative, which suggests an absence in the overall estimates of positive confounding by smoking.

There was however, some evidence that the ERR/Sv risk estimate for white-collar workers was higher than for blue-collar workers for IHD ($P = 0.03$), and it is perhaps notable that a not dissimilar pattern was seen for COPD with a higher ERR/Sv seen for white-collar than blue-collar workers ($P = 0.03$), and in both cases the higher white-collar estimates were driven by associations among the professional/technical group. Although the overall confounding effect of smoking would appear to be small, that does not preclude smoking as having a confounding effect within subgroups of the cohort. However, it is important to recognize the limitations of the socioeconomic coding information available for this analysis: only a single socioeconomic value was assigned to workers throughout the entire follow-up; for some employers/facilities this will relate to socioeconomic status at first hire, while for others it will relate to status at leaving work. In reality a number of workers will have moved among socioeconomic groups during their years of employment and the higher ERR/Sv estimates seen for IHD and COPD in the white-collar workers may well be an artefact of these limitations rather than anything to do with smoking. For example, we may be comparing professional/technical staff at hire with professional/technical staff at end of employment who may have very different background mortality rates and, importantly, dose distributions. Unfortunately, with data available for this study, this issue cannot currently be readily examined.

Socioeconomic status is clearly an important confounder in this study, with the ERR/Sv estimates for circulatory disease more than doubling when adjustment for differences in background rates among different socioeconomic groups is not included in the model (Table 6). Socioeconomic status is not only an important discriminating factor for non-cancer mortality experienced in this cohort; it is also an important indicator for many of the known risk factors for circulatory system disease mentioned above, including diabetes, obesity, hypertension and high levels of blood LDL. In the absence of detailed information on these specific risk factors, the current study has attempted to partially control for some of these risks factors through adjustment for socioeconomic status in the analysis. However, by their very nature, surrogate measurements for these risk factors are not as good as actual measurements and some residual confounding is likely. Nevertheless, in a recent review on circulatory disease and radiation effects (16), in those studies that had additional information on some of these risk factors (9, 34–36), ERR/Sv estimates were virtually unchanged when additional adjustment for these factors was made.

Duration of employment was considered to be a possible confounder and was therefore included in the main analysis to control for the so-called “healthy worker survivor effect” (46). This effect can result in negative confounding when workers who are healthier and therefore have lower mortality rates stay in employment longer and may accumulate higher doses (47). When we removed adjustment for duration of employment in the analyses, risk estimates reduced in magnitude, indicating that a healthy worker survivor effect may be present in this cohort. For circulatory diseases, there was little evidence of effect modification with duration of employment (a proxy for length of exposure), and this is

perhaps indicative that dose rate may not be an important contributing factor in the pattern of risks observed.

Importantly, the current study relies on cause of death information that is routinely collected in all three countries. The sensitivity and specificity of the death certificate as a proxy for information on disease incidence is less than ideal. For some conditions, particularly those that are common in older adults, that they may die with (but not from), the death certificate may have low sensitivity. In prior studies, it has been found that the positive predictive value of cause of death information tends to be better for broader groups of outcomes than specific codes, and this could potentially explain some of patterns of risk that we see in these cohorts.

The mechanisms by which low-dose and low-dose-rate exposure to ionizing radiation might cause circulatory disease are unclear. Possible mechanisms to explain radiation effects on circulatory disease have been examined in recent reviews (4–7, 48). A postulated mechanism suggests an inflammatory response to cellular damage from radiation exposure, which could potentially have implications for induction of other types of disease. An argument against this is that while acute doses (above 1 Gy) are considered to have an inflammatory effect, lower doses (below 0.5 Gy) have been recognized as having potentially anti-inflammatory properties that could possibly slow the progression of circulatory diseases (49–50). A recent ICRP report classified circulatory diseases as a tissue reaction effect with a threshold for the effect of 0.5 Gy (51). At doses below this level, evidence was not considered sufficient to conclude a causative relationship between circulatory disease and ionizing radiation. In this study, significant risks for circulatory disease were detected down to slightly lower dose levels (0.3 Gy), which tallies with findings from a recent review of circulatory disease (52) that concluded there may be a radiation-induced effect even at low doses.

Another potential mechanism suggests that doses of ionizing radiation induce the formation of atherosclerotic plaques (53). It has also been observed that junctions between endothelial cells are significantly weakened by radiation; this increases the permeability of the endothelial monolayer to macro-molecules such as LDL and potentially to the migration of monocytes. Although these effects are caused by radiation-damaging cellular DNA, this mechanism does not involve mutation of the genetic code. Currently, such a process is speculative; but such a mechanism would provide a possible explanation for some of differences in risks that we see among cohorts. At the moment, however, biological mechanisms that might plausibly cause effects at low dose need to be given further consideration before any causal interpretation can be drawn.

Circulatory disease is a major cause of death in the general population and accounts for 42% of all deaths in the INWORKS cohorts. If a relationship between radiation exposure and circulatory disease did prove to be causal, then this would be an important public health and radiation protection concern, given the increasing use of higher dose diagnostic procedures such as CT scans and other radiation therapies. However, it is important to bear in mind that workers in this study are predominately exposed to very low doses, and workers at the median dose level (3.5 mSv) show only an increase in relative rate of less than 0.1% when the linear model is used. To put the risks observed for circulatory disease in context with the

results obtained for cancers in these cohorts, the predicted number of circulatory disease excess deaths potentially attributable to external radiation exposure using the linear ERR model (218 deaths 95% CI: 55, 387) was virtually identical to the predicted number of excess cancer deaths (209 deaths) attributable to external radiation.

CONCLUSIONS

To date, the evidence of an effect of radiation exposure on circulatory diseases has been equivocal at low doses. This study provides further evidence that non-cancer mortality risks may be increased by low-dose and low-dose-rate radiation exposure particularly for heart diseases and cerebrovascular diseases. The risks are generally consistent with those observed in the A-bomb survivor studies; significant associations are observed at relatively low doses, with those for circulatory disease detected down to 0.3 Sv. However, some heterogeneity in the risks was observed, which warrants further investigation before any firmer conclusions are drawn. Further follow-up of this or other cohorts, incorporating information on internal exposure and other potential confounders associated with lifestyle and other factors, may prove informative as we work to understand the potential biological mechanisms that might cause these non-cancer effects. Although these risks have been observed among radiation workers, any potential association between radiation exposure and increased non-cancer disease risk is an important issue to radiation protection and public health, given the widespread use of radiation in medical procedures today.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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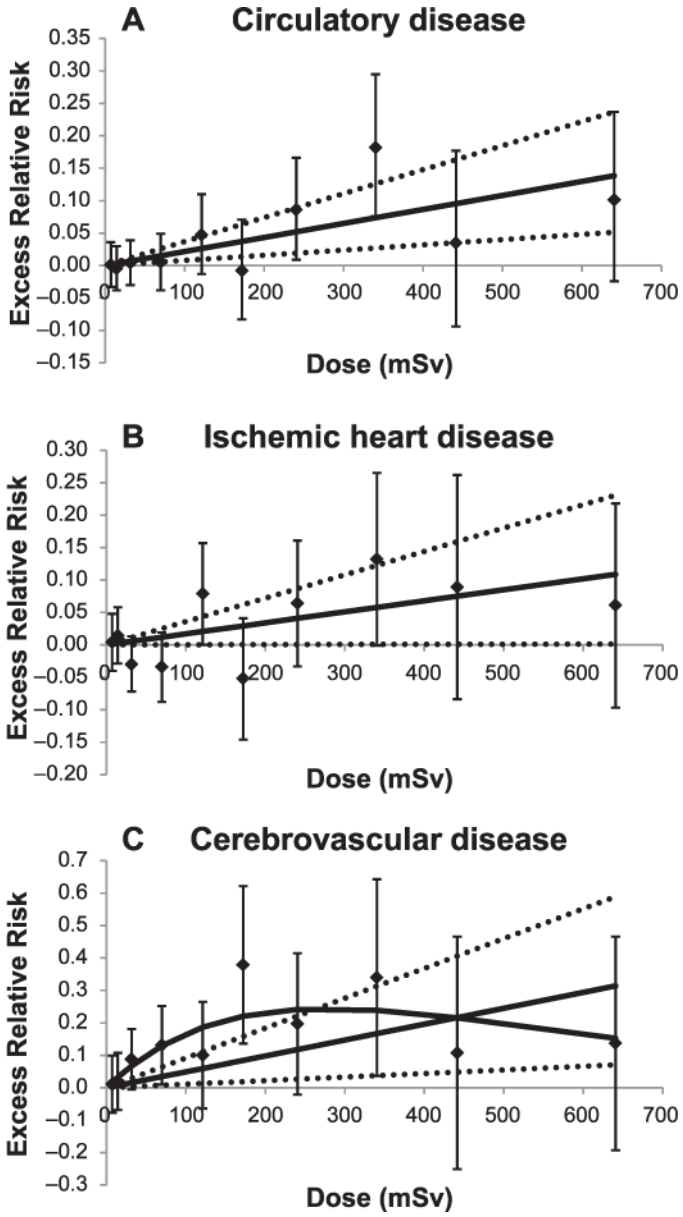

FIG. 1.

Mortality from circulatory diseases (panel A), ischemic heart diseases (panel B) and cerebrovascular diseases (panel C): ERR estimates and 90% CI by 10-year lagged external dose category with linear ERR/Sv estimate and associated 90% CI reference lines. Also shown is the linear exponential dose response observed for cerebrovascular disease.

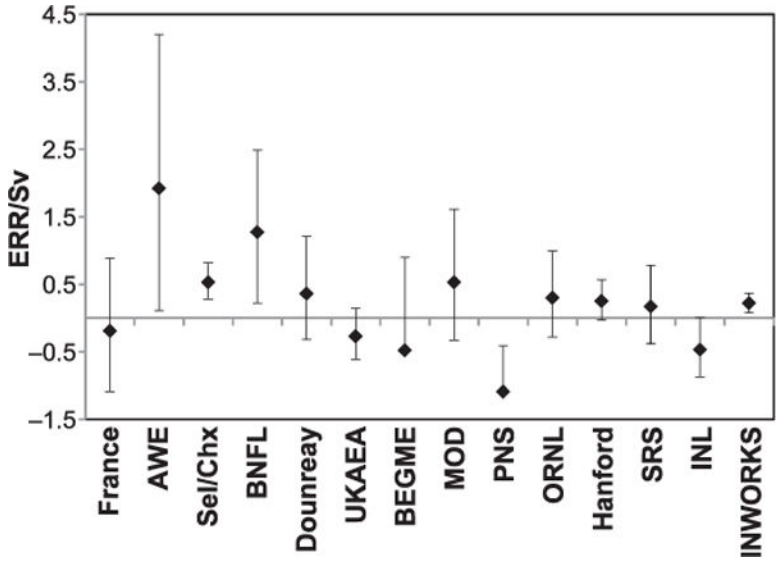

FIG. 2.

Mortality from circulatory disease by employer/facility: linear ERR estimates and 90% CI.

TABLE 1

Summary of Cohorts Included in the INWORKS Study

Country, cohort[a]	Follow-up period	No. of workers by cumulative Hp(10) dose (mSv)						Total no. of workers	Collective dose (Sv)	Mean dose (mSv)	Person-years	Non-cancer deaths	Circulatory disease deaths
		<10	10–50	50–	100–	200–	≥400						
France[b]	1968–2004	40,079	12,450	3,821	2,056	551	46	59,003	1,084.6	18.4	1,469,661	3,533	1,483
UK, AWE	1955–2001	11,422	2,177	265	105	46	10	14,025	120.0	8.6	275,066	1,973	1,342
UK, Sel/Chx[c]	1955–2001	6,013	6,272	2,830	2,523	1,780	1,155	20,573	1,946.7	94.6	494,808	3,031	2,137
UK, BNFL[d]	1955–2001	9,211	4,871	1,187	483	82	13	15,847	319.6	20.2	405,722	3,286	2,231
UK, Dounreay	1955–2001	2,057	2,176	734	461	289	81	5,798	304.0	52.4	154,985	1,054	713
UK, UKAEA[e]	1955–2001	10,137	5,733	1,546	856	413	203	18,888	627.3	33.2	555,775	3,594	2,382
UK, BEGME	1958–2001	6,830	5,991	1,488	692	137	6	15,144	401.8	26.5	346,754	1,611	1,091
UK, MOD	1961–2001	49,137	5,811	1,380	788	317	60	57,493	529.3	9.2	1,176,086	3,035	1,785
U.S., PNS	1952–2005	6,101	2,075	686	439	179	6	9,486	221.4	23.3	296,856	3,397	2,109
U.S., ORNL	1944–2005	10,148	2,896	574	353	188	69	14,228	266.1	18.7	533,785	3,906	2,232
U.S., Hanford	1944–2005	17,573	6,918	1,615	1,136	854	333	28,429	897.0	31.6	1,037,651	9,057	5,603
U.S., SRS	1950–2005	13,027	4,243	1,167	1,000	573	15	20,025	513.0	25.6	648,984	3,888	2,260
U.S., INL	1949–2005	21,560	4,789	1,514	902	389	106	29,260	538.8	18.4	824,050	4,658	2,474
Total	1944–2005	203,368	66,421	18,811	11,794	5,798	2105	308,297	7,771.5	25.2	8,221,876	46,029	27,848

[a] Cohort employer/facilities in this table represent the subdivision of cohorts by employer/facility used in the main analysis.

[b] Data for France represent the combined totals for the CEA, AREVA and EDF cohorts.

[c] For analysis purposes, the Sel/Chx data represent combined data for the Chapelcross and Sellafield sites.

[d] BNFL data represent the combined data for the BNFL sites excluding Sellafield/Chapelcross.

[e] UKAEA data represent the combined data for the UKAEA sites excluding Dounreay.

TABLE 2

Mortality from Non-Cancer Disease in Relationship to External Radiation Dose: ERR/Sv Estimates, Observed and Expected[a] Number of Deaths from the Poisson Regression Analysis

	Observed deaths (expected deaths) by cumulative external dose (mSv), 10-year lag													
Cause of death	**<5**	**5–10**	**10–20**	**20–50**	**50–100**	**100–150**	**150–200**	**200–300**	**300–400**	**400–500**	**>500**	**Total**	**ERR/Sv[b] (90% CI)**	***P* value[c]**
Infectious diseases	307 (322.7)	73 (54.0)	52 (54.1)	56 (56.3)	26 (30.8)	15 (14.3)	10 (7.8)	12 (8.1)	0 (3.8)	0 (1.9)	2 (2.0)	553 (555.7)	0.19 (<0, 1.08)	0.621
Endocrine diseases	642 (614.3)	118 (125.5)	128 (131.5)	131 (136.2)	62 (75.4)	43 (36.8)	26 (21.1)	25 (23.1)	10 (11.9)	3 (6.4)	14 (6.8)	1,202 (1,188.8)	0.34 (−0.28, 1.13)	0.196
Blood diseases	100 (104.4)	16 (22.8)	30 (25.3)	25 (27.2)	20 (15.2)	7 (6.9)	5 (4.0)	6 (4.2)	2 (2.3)	0 (1.3)	0 (1.6)	211 (215.3)	−0.56 (<0, 1.30)	0.784
Mental disorders	340 (335.8)	73 (72.9)	72 (79.7)	90 (83.3)	43 (44.8)	33 (20.8)	14 (11.7)	22 (12.6)	8 (6.8)	3 (3.5)	7 (4.2)	705 (676.2)	1.30 (0.23, 2.72)	0.019
Nervous system	715 (729.3)	151 (164.0)	189 (181.4)	207 (191.4)	108 (103.7)	45 (49.0)	28 (28.1)	26 (30.2)	17 (16.1)	10 (9.1)	9 (10.4)	1505 (1,512.7)	−0.15 (<−0.68, 0.50)	0.657
Circulatory diseases	13,185 (13,176.7)	3,006 (3,007.0)	3,261 (3,266.6)	3,627 (3,597.6)	1,961 (1,944.8)	944 (900.9)	509 (511.6)	606 (558.4)	356 (300.3)	171 (164.8)	222 (201.4)	27,848 (27,630.0)	0.22 (0.08, 0.37)	0.004
Respiratory diseases	2,381 (2,394.4)	572 (596.9)	666 (656.5)	737 (716.8)	398 (382.1)	177 (176.1)	109 (100.4)	115 (108.8)	58 (60.6)	33 (33.4)	45 (39.4)	5,291 (5,265.5)	0.13 (−0.17, 0.47)	0.243
Digestive diseases	1,145 (1,155.7)	215 (219.5)	243 (230.6)	280 (252.9)	129 (138.4)	45 (63.8)	44 (35.5)	38 (37.3)	16 (18.6)	11 (9.5)	14 (10.7)	2,180 (2,172.7)	0.11 (−0.36, 0.69)	0.358
Genitourinary diseases	365 (346.6)	73 (77.7)	81 (83.1)	85 (86.7)	42 (46.4)	18 (21.9)	10 (12.5)	10 (13.7)	7 (7.6)	4 (4.0)	6 (4.8)	701 (705.0)	−0.17 (<−0.77, 0.65)	0.652
Muscoskeletal disease	99 (100.6)	27 (22.9)	20 (26.0)	26 (27.5)	20 (14.4)	7 (6.8)	4 (3.8)	6 (4.2)	2 (2.3)	1 (1.3)	2 (1.8)	214 (211.6)	0.31 (<−1.27, 2.78)	0.380
Ill-defined diseases	552 (582.3)	115 (101.6)	115 (108.7)	135 (117.3)	56 (60.8)	23 (25.8)	11 (13.6)	14 (13.4)	8 (6.4)	3 (3.4)	4 (4.4)	1,036 (1,037.8)	−0.07 (<−0.81, 0.92)	0.553
External causes	2,934 (2,917.5)	363 (346.1)	350 (349.3)	384 (373.1)	214 (196.7)	77 (84.5)	45 (45.2)	47 (44.6)	22 (20.4)	7 (10.0)	8 (9.9)	4,451 (4,397.5)	−0.12 (<−0.60, 0.45)	0.642
All non-cancers[d]	22,843 (22,909.2)	4,814 (4,828.1)	5,216 (5,205.3)	5,795 (5,676.8)	3,087 (3,058.7)	1,439 (1,409.5)	817 (796.5)	931 (859.4)	508 (457.1)	246 (248.3)	333 (297.0)	46,029 (45,746.0)	0.19 (0.07, 0.30)	0.003

[a] The expected numbers of deaths is the estimated number of background deaths using the Poisson regression model in the absence of occupational radiation exposure

[b] ERR/Sv estimates are calculated from a linear ERR model that contains background adjustments for age, birth-cohort, gender, socioeconomic status, duration of employment and facility of employment.

[c] P value represents a one-sided test of the linear ERR/Sv parameter.

[d] Diseases with fewer than 100 deaths have not had risk estimates calculated, although these diseases are included in the all non-cancers grouping; this includes skin disease (50 deaths), congenital malformations (79 deaths) and other diseases (3 deaths).

TABLE 3

Mortality from Circulatory Diseases, Ischemic Heart Diseases and Cerebrovascular Diseases: Effect of Restricting Dose Range on Linear ERR/Sv Estimates

	Circulatory diseases		Ischemic heart diseases		Cerebrovascular diseases	
	N	**ERR/Sv (90% CI)**	**N**	**ERR/Sv (90% CI)**	**N**	**ERR/Sv (90% CI)**
Overall[a]	27,570	0.22 (0.08, 0.37)	17279	0.17 (0.002, 0.36)	4399	0.49 (0.11, 0.92)
Restricting dose range						
<500 mSv	27,348	0.28 (0.10, 0.47)	17138	0.23 (0.01, 0.47)	4,362	0.86 (0.35, 1.43)
<400 mSv	27,177	0.36 (0.15, 0.58)	17021	0.24 (−0.10, 0.50)	4,334	1.13 (0.54, 1.78)
<300 mSv	26,822	0.28 (0.03, 0.53)	16800	0.16 (−0.15, 0.48)	4,273	1.26 (0.55, 2.05)
<200 mSv	26,216	0.19 (−0.14, 0.53)	16412	0.01 (−0.39, 0.44)	4,176	1.78 (0.83, 2.83)
<150 mSv	25,711	0.36 (−0.07, 0.79)	16100	0.25 (−0.27, 0.80)	4,074	1.41 (0.26, 2.67)
<100 mSv	24,771	0.14 (−0.45, 0.76)	15477	−0.56 (<0, 0.19)	3,927	2.07 (0.43, 3.80)
<50 mSv	22820	0.15 (−0.96, 1.30)	14272	−0.70 (<0, 0.72)	3,593	2.32 (−0.59, 5.50)

[a]For overall results, the ERR/Sv estimates are calculated from a linear ERR model that contains background adjustments for age, birth-cohort, gender, socioeconomic status, duration of employment and facility of employment.

TABLE 4

Mortality from Circulatory Diseases, Ischemic Heart Diseases and Cerebrovascular Diseases, Variation in Linear ERR/Sv by Attained Age, Gender, Duration of Employment and Socioeconomic Status

	Circulatory diseases		Ischemic heart diseases		Cerebrovascular diseases	
	N	**ERR/Sv (90% CI)**	**N**	**ERR/Sv (90% CI)**	**N**	**ERR/Sv (90% CI)**
Overall[a]	27,570	0.22 (0.08, 0.37)	17,279	0.17 (0.002, 0.36)	4,399	0.49 (0.11, 0.92)
Gender						
Male	25,862	0.20 (0.07, 0.36)	16,515	0.16 (–0.01, 0.34)	3,969	0.48 (0.10, 0.91)
Female	1,708	4.22 (1.72, 7.21)	764	6.17 (2.44, 10.92)	430	2.67 (<0, 9.79)
Test for heterogeneity[b]		$P = 0.005$		$P = 0.004$		$P > 0.50$
Attained age (years)						
<60	6,075	0.59 (0.15, 1.08)	4,402	0.64 (0.14, 1.20)	659	0.06 (<0, 1.99)
60–69	7,375	0.05 (−0.20, 0.31)	4,969	−0.02 (−0.30, 0.29)	970	−0.18 (<0, 0.72)
≥70	14,120	0.23 (0.06, 0.41)	7,908	0.18 (−0.04, 0.41)	2,770	0.66 (0.22, 1.17)
Test for heterogeneity[b]		$P = 0.21$		$P = 0.17$		$P = 0.33$
Duration of employment (years)						
<10	10,526	0.27 (−0.31, 0.90)	6,564	0.04 (−0.67, 0.83)	1,708	1.01 (−0.58, 2.90)
10–19	7,470	0.15 (−0.14, 0.47)	4,690	0.17 (−0.19, 0.57)	1,259	0.35 (−0.34, 1.19)
20–29	6,227	0.27 (0.06, 0.49)	3,946	0.16 (−0.09, 0.42)	971	0.70 (0.16, 1.35)
≥30	3,347	0.19 (−0.03, 0.42)	2,079	0.21 (−0.06, 0.51)	461	0.21 (−0.36, 0.94)
Test for heterogeneity[b]		$P > 0.50$		$P > 0.50$		$P > 0.50$
Socioeconomic grouping						
Blue-collar	18,846	0.17 (0.01, 0.33)	11,976	0.07 (−0.11, 0.27)	2,965	0.59 (0.18, 1.07)
White-collar	8,724	0.42 (0.13, 0.74)	5,303	0.58 (0.22, 0.98)	1,434	−0.08 (<0, 0.77)
Test for heterogeneity[b]		$P = 0.18$		$P = 0.03$		$P = 0.20$

[a]For the overall results, the ERR/Sv estimates are calculated from a linear ERR model that contains background adjustments for age, birth-cohort, gender, socioeconomic status, duration of employment and facility of employment.

[b]Test for heterogeneity is based on the likelihood ratio test comparing the overall model with models that allow the ERR to vary by gender, attained age, duration of employment or socioeconomic status.

TABLE 5

Mortality from Circulatory Diseases, Ischemic Heart Diseases and Cerebrovascular Diseases: Temporal Variation in Linear ERR/Sv Estimates by Age at Exposure, Time since Exposure and Using Differing Lagging Strategies

	Circulatory diseases ERR/Sv (90% CI)	Ischemic heart diseases ERR/Sv (90% CI)	Cerebrovascular diseases ERR/Sv (90% CI)
Overall[a]	0.22 (0.08, 0.37)	0.17 (0.002, 0.36)	0.49 (0.11, 0.92)
Age at exposure			
<35 years	0.26 (<0, 2.76)	−0.87 (<0, 1.98)	3.54 (<0, 13.08)
35–50 years	0.39 (0.02, 0.77)	0.51 (0.06, 0.98)	0.10 (<0, 1.35)
≥50 years	0.14 (−0.03, 0.32)	0.07 (−0.14, 0.30)	0.47 (0.02, 0.97)
Test for heterogeneity[b]	$P > 0.50$	$P = 0.38$	$P > 0.50$
Time since exposure			
10–20 years ago	0.28 (−0.08, 0.66)	0.54 (0.10, 1.01)	0.28 (<0, 1.40)
20–30 years ago	0.40 (0.04, 0.78)	0.23 (−0.21, 0.69)	0.48 (−0.44, 1.50)
≥30 years ago	−0.06 (−0.35, 0.25)	−0.25 (−0.61, 0.15)	0.50 (−0.24, 1.35)
Test for heterogeneity[b]	$P = 0.27$	$P = 0.06$	$P > 0.50$
Alternative lagging strategies			
Lag time			
2 years	0.09 (−0.03, 0.22)	0.06 (−0.09, 0.22)	0.32 (−0.02, 0.70)
5 years	0.13 (0.004, 0.27)	0.10 (−0.06, 0.26)	0.39 (0.04, 0.79)
10 years	0.22 (0.08, 0.37)	0.17 (0.002, 0.36)	0.49 (0.11, 0.92)
15 years	0.29 (0.13, 0.46)	0.24 (0.04, 0.45)	0.55 (0.14, 1.03)
20 years	0.30 (0.12, 0.49)	0.18 (−0.04, 0.42)	0.60 (0.14, 1.14)

[a]For overall results, the ERR/Sv estimates are calculated from a linear ERR model that contains background adjustments for age, birth-cohort, gender, socioeconomic status, duration of employment and facility of employment.

[b]Test for heterogeneity is based on the likelihood ratio test comparing overall model using 10-year-lag cumulative doses with models that partition the 10-year-lag dose into three time windows based on either age at exposure or time since exposure.

TABLE 6

Mortality from Circulatory Diseases, Ischemic Heart Diseases and Cerebrovascular Diseases: Sensitivity Analyses for Potential Effect of Non-Photon Exposures and Alternative Background Models on Linear ERR/Sv Estimates

	Circulatory diseases		Ischemic heart diseases		Cerebrovascular diseases	
	N	**ERR/Sv (90% CI)**	**N**	**ERR/Sv (90% CI)**	**N**	**ERR/Sv (90% CI)**
Overall[a]	27,570	0.22 (0.08, 0.37)	17279	0.17 (0.002, 0.36)	4,399	0.49 (0.11, 0.92)
Internal monitoring[a]						
No	22,299	0.12 (−0.09, 0.33)	13788	0.05 (−0.20, 0.32)	3,506	0.33 (−0.24, 0.99)
Yes	5,271	0.43 (0.21, 0.69)	3491	0.43 (0.16, 0.74)	893	0.75 (0.17, 1.50)
Test for heterogeneity[b]		$P = 0.09$		$P = 0.10$		$P = 0.43$
Neutron exposure status						
No significant neutron exposure	26,612	0.21 (0.07, 0.37)	16697	0.16 (−0.01, 0.35)	4243	0.44 (0.06, 0.88)
Neutron dose >10% of gamma dose	958	0.51 (−0.12, 1.30)	582	0.56 (−0.26, 1.63)	156	1.87 (−0.23, 5.51)
Test for heterogeneity[b]		$P = 0.48$		$P = 0.47$		$P = 0.32$
Alternative background models						
Remove SES		0.51 (0.35, 0.67)		0.46 (0.27, 0.67)		0.78 (0.36, 1.26)
Remove duration of employment		0.07 (−0.06, 0.20)		0.07 (−0.08, 0.29)		0.18 (−0.13, 0.54)
Country rather than facility		0.43 (0.29, 0.58)		0.41 (0.24, 0.59)		0.99 (0.58, 1.44)
Main employer rather than facility[c]		0.32 (0.18, 0.46)		0.31 (0.14, 0.50)		0.60 (0.22, 1.02)
Include internal monitoring status		0.27 (0.12, 0.43)		0.24 (0.05, 0.44)		0.55 (0.13, 1.03)
Include neutron exposure status		0.23 (0.08, 0.38)		0.18 (0.01, 0.36)		0.49 (0.11, 0.93)

[a]For the overall results the ERR/Sv estimates are calculated from a linear ERR model that contains background adjustments for age, birth-cohort, gender, socioeconomic status, duration of employment and facility of employment.

[b]Test for heterogeneity is based on the likelihood ratio test, comparing the model that contains an additional background adjustment for internal monitoring status or neutron exposure status with models that allow the ERR to vary by internal monitoring status or neutron exposure status. In the overall model, background rate was adjusted for 15 levels of employer/facility and in this case the background rate was only adjusted by the 13-level factor of main employer.

TABLE 7

Comparison of ERR/Sv Estimates between the INWORKS Study, the Life Span Study (LSS) and the 15-Country Study

	LSS cohort (1950–2003)[a]		INWORKS cohort (1944–2005)[b]		15-country study (1944–1997)[d]	
Cause of death	**Deaths**	**ERR/Sv (90% CI)**	**Deaths**	**ERR/Sv (90% CI)**	**Deaths**	**ERR/Sv (95% CI)**
Circulatory diseases	15,391	0.12 (0.05, 0.18)	27,570	0.22 (0.08, 0.37)	8,412	0.09 (−0.43, 0.70)
Heart diseases[c]	6,976	0.18 (0.08, 0.28)	20,564	0.18 (0.02, 0.35)	5,821	−0.01 (−0.59, 0.69)
Cerebrovascular diseases	7,708	0.08 (−0.003, 0.18)	4,399	0.49 (0.11, 0.92)	1,224	0.88 (−0.67, 3.16)
Respiratory diseases	4,143	0.16 (0.06, 0.29)	5,241	0.13 (−0.17, 0.47)	792	1.16 (−0.53, 3.84)
Digestive diseases	2,379	0.07 (−0.06, 0.23)	2,154	0.14 (−0.34, 0.72)	620	0.96 (<0, 4.52)
External causes	1,350	−0.13 (−0.30, 0.06)	4,387	−0.13 (<−0.6, 0.43)	2,060	−0.50 (<0, 1.08)
Circulatory excluding cerebrovascular	7,683	0.16 (0.07, 0.25)	23,171	0.17 (0.02, 0.33)	–	–

[a] For comparison purposes, risks are calculated using colon dose and including adult survivors exposed between 20 and 60 years of age and with a colon dose of <2 Gy, employing the linear models and data from Osaza *et. al.* (7).

[b] Risks calculated using Hp(10) doses.

[c] For comparison purposes the INWORKS heart disease data in this table include ischemic heart disease and other heart diseases combined.

[d] The 15-country study results are taken from Vrijheid *et. al.* (27) using colon doses and the heart disease result represents the ERR/Sv for ischemic heart alone.