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Mark P. Little,^{1*} Tamara V. Azizova,² Dimitry Bazyka,³ Simon D. Bouffler,⁴ Elisabeth Cardis,⁵ Sergey Chekin,⁶ Vadim V. Chumak,³ Francis A. Cucinotta,⁷ Florent de Vathaire,⁸ Per Hall,⁹ John D. Harrison,⁴ Guido Hildebrandt,^{10, 11} Victor Ivanov,⁶ Valeriy V. Kashcheev,⁶ Sergiy V. Klymenko,³ Michaela Kreuzer,¹² Olivier Laurent,¹³ Kotaro Ozasa,¹⁴ Thierry Schneider,¹⁵ Soile Tapio,¹⁶ Andrew M. Taylor,¹⁷ Ioanna Tzoulaki,¹⁸ Wendy L. Vandoolaeghe,¹⁸ Richard Wakeford,¹⁹ Lydia B. Zablotska,²⁰ Wei Zhang,⁴ Steven E. Lipshultz²¹

¹Radiation Epidemiology Branch, National Cancer Institute, Rockville, USA

²Southern Urals Biophysics Institute, Ozyorsk, Russia

³Research Center for Radiation Medicine, Kyiv, Ukraine

⁴Health Protection Agency, Centre for Radiation, Chemical and Environmental Hazards, Chilton, UK

⁵Center for Research in Environmental Epidemiology (CREAL), Barcelona, Spain

⁶Medical Radiological Research Center of Russian Academy of Medical Sciences, Obninsk, Russia

⁷NASA Johnson Space Center, Space Radiation Program, Houston, USA

⁸Radiation Epidemiology Group, INSERM Unité U1018, Institut Gustave Roussy, Villejuif, France

⁹Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden

¹⁰Department of Radiotherapy and Radiation Oncology, University of Leipzig, Leipzig, Germany

¹¹Department of Radiotherapy and Radiation Oncology, University of Rostock, Rostock, Germany

¹²Federal Office for Radiation Protection, Department of Radiation Protection and Health, Oberschleissheim, Germany

¹³Laboratoire d'Epidémiologie, Institut de Radioprotection et de Sûreté Nucleaire, Fontenay-aux-Roses, France

¹⁴Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima City, Japan

¹⁵CEPN (Nuclear Evaluation Protection Center), Fontenay-aux-Roses, France

¹⁶Helmholtz Zentrum München, German Research Centre for Environmental Health, Institute of Radiation Biology (ISB), Radiation Proteomics, Oberschleissheim, Germany

¹⁷UCL Institute of Cardiovascular Sciences & Great Ormond Street Hospital for Children, London, UK

¹⁸Department of Epidemiology and Biostatistics, Imperial College Faculty of Medicine, London, UK

¹⁹Dalton Nuclear Institute, University of Manchester, Manchester, UK

²⁰Department of Epidemiology and Biostatistics, University of California San Francisco School of Medicine, San Francisco, USA

²¹Department of Pediatrics, Leonard M. Miller School of Medicine, University of Miami, USA

*Corresponding author:

Mark P. Little

Radiation Epidemiology Branch

National Cancer Institute, Executive Plaza South,

6120 Executive Boulevard MSC 7238, Rockville, MD 20852-7238 USA

Tel +1 301 402 9138 (office) / +1 301 875 3413 (mobile)

Fax +1 301 402 0207

E-mail mark.little@nih.gov

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Abbreviations: Advisory Group on Ionising Radiation (AGIR); confidence interval (CI); excess absolute risk (EAR); excess relative risk (ERR); ischemic heart disease (IHD); Radiation Effects Research Foundation (RERF); radiation exposure-induced death (REID); United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR).

ABSTRACT

Background Although high doses of ionizing radiation have long been linked to circulatory disease, evidence for an association at lower exposures remains controversial. However, recent analyses suggest excess relative risks at occupational exposure levels.

Objectives We performed a systematic review and meta-analysis to summarize information on circulatory disease risks associated with moderate- and low-level whole-body ionizing radiation exposures.

Methods We conducted Medline/ISI Thompson searches of peer-reviewed papers published since 1990 using the terms “radiation”+“heart”+“disease” or “radiation”+“stroke” or “radiation”+“circulatory”+“disease”. Radiation exposures had to be whole-body, with cumulative mean dose <0.5 Sv, or at low dose rate (<10 mSv per day). We estimated population risks of circulatory disease from low-level radiation exposure using excess relative risk estimates from this meta-analysis and current mortality rates for nine major developed countries.

Results Estimated excess population risks for all circulatory diseases combined ranged from 2.5% per Sv (95% confidence interval (CI) 0.8 to 4.2) for France to 8.5% per Sv (95% CI 4.0 to 13.2) for Russia.

Conclusions Our review supports an association between circulatory disease mortality and low and moderate doses of ionizing radiation. Our analysis was limited by heterogeneity among studies (particularly for non-cardiac endpoints), the possibility of uncontrolled confounding in some occupational groups by lifestyle factors, and higher dose groups (>0.5 Sv) generally driving the observed trends. If confirmed, our findings suggest that overall radiation-related mortality is about twice that currently estimated based on estimates for cancer endpoints alone (which range from 4.2% to 5.6% per Sv for these populations).

INTRODUCTION

Based on observations in irradiated populations, the health risks of low-level exposure to ionizing radiation have been assumed to be related primarily to cancer. At high radiation doses a variety of other well-established effects are observed, in particular damage to the structures of the heart and to the coronary, carotid, and other large arteries. This damage occurs both in patients receiving radiotherapy and in experimental animals (Adams et al. 2003). There are plausible, if not completely understood, mechanisms by which high doses of radiation affect the blood circulatory system (Schultz-Hector and Trott 2007). Recent analyses of the Japanese atomic-bomb survivors suggested that excess mortality from non-cancer disease was comparable to that from cancer (Ozasa et al. 2012; Preston et al. 2003).

An association between lower doses (< 0.5 Gy) and late circulatory disease has only recently been suspected and remains controversial. Recent reviews present evidence suggesting an excess radiation-induced risk at occupational and environmental dose levels (Advisory Group on Ionising Radiation (AGIR) 2010; Little et al. 2010). In particular, a review by the Health Protection Agency's Advisory Group on Ionising Radiation (AGIR) in the United Kingdom estimated substantial excess risks for ischemic heart disease and stroke, but concluded that a significantly elevated risk was detectable only for exposures above about 0.5 Gy (AGIR 2010). The AGIR report also reviewed biological data suggesting that many inflammatory endpoints potentially relevant to circulatory disease may be differentially regulated below and above about 0.5 Gy (AGIR 2010), emphasizing the importance of assessing risks associated with exposures < 0.5 Gy.

Here, we test the hypothesis of a causal association between low-level radiation exposure and circulatory disease in a general unselected population. We estimate population circulatory disease mortality risks from low doses of radiation by extending recent meta-analyses (AGIR 2010; Little et al. 2008; Little et al. 2009b; Little et al. 2010) of Japanese

atomic-bomb survivors and occupationally exposed groups, taking heterogeneity among studies into account. The results of the meta-analysis are used to estimate the potential radiation-related mortality risks of circulatory disease in various populations and compare them with the risks of cancer (AGIR 2010; Little et al. 2008; Little et al. 2009b; Little et al. 2010).

DATA AND METHODS

Data and meta-analysis

Searches of the Medline and ISI Thompson (Web of Knowledge) databases were conducted on May 14, 2011 and August 17, 2011, respectively, using the terms “radiation” + “heart” + “disease”, or “radiation” + “stroke”, or “radiation” + “circulatory” + “disease”. The ISI Thompson database search was restricted to human data. Only peer-reviewed papers from 1990 onwards that had reliable ascertainment of circulatory disease morbidity or mortality were considered; abstracts and letters were not included. There was no restriction on the type of study design (cohort, case-control, case-base etc). Abstracts and papers were manually reviewed by MPL and WZ. A total of 4971, 1180 and 526 articles were published in Medline in these categories since 1990; the ISI Thompson search (which was conducted using all three groups of search words combined) returned a total of 1480 articles. Although there was no restriction to publication in English, based on assessment of the titles and abstracts the only studies meeting our criteria were published in that language.

Studies were excluded if there was no analysis of circulatory disease in relation to individual exposures, or if there was not a reliable (e.g., film-badge or area-monitoring based) estimate of whole-body dose. All of the studies included in the analysis expressed radiation dose in sieverts (Sv), which should be very similar to unweighted absorbed doses in gray (Gy) (ICRP 2007). Exposures had to involve moderate or low dose (cumulative mean < 0.5 Sv) whole-

body exposure, or exposures at a low dose rate (<10 mSv per day) and so included studies of environmental exposures, occupational exposures, or exposures experienced by Japanese atomic-bomb survivors. The reason for emphasizing uniform whole-body exposure is that the target tissue for radiation-associated circulatory disease is not known, so whole-body dose (which will be approximately the same as dose to any tissue (ICRP 2007)) is the most reliable metric with which to compare studies. However, we also included two occupationally-exposed groups with some degree of non-uniformity in exposure (e.g., in relation to liver, lung, and bone dose), although with uniform dose to the circulatory system (Azizova et al. 2010a; Azizova et al. 2010b; Kreuzer et al. 2006). The requirement for uniform whole-body dose and analysis of circulatory disease in relation to individual dose resulted in the exclusion of a number of otherwise eligible studies, for example the Massachusetts tuberculosis fluoroscopy cohort (Davis et al. 1989).

We excluded studies of any cohort in which the additional follow-up amounts to a year or less with respect to the larger analysis in which it is included. Therefore we excluded US and Canadian nuclear worker studies (Howe et al. 2004; Zablotska et al. 2004) that had no more follow-up (to 31/12/1997 and 31/12/1994 respectively) than the International Agency for Research on Cancer 15-country study (Vrijheid et al. 2007) which subsumed them. We also excluded the Canadian National Dose Registry study (Zielinski et al. 2009) that overlaps with the Canadian nuclear worker data (Zablotska et al. 2004) and with somewhat lower quality of linkage to employment records and verification of dosimetry (Gilbert 2001), and a study by Atkinson *et al.* (2004) subsumed within the latest National Registry for Radiation Workers analysis cohort (Muirhead et al. 2009) and with earlier final follow-up (end 1997 compared with end 2001). Recent analyses of circulatory and related endpoints in the Japanese atomic-bomb survivor cohort that were published after our literature search were also not included (Adams et al. 2012; Ozasa et al. 2012; Takahashi et al. 2011; Takahashi et al. 2012); the mortality study of Ozasa *et al.* (2012) had identical follow-up (1950-2003) to an earlier paper by Shimizu *et al.* (2010) that was

included in our analysis.

Having derived the primary study populations, we further selected studies so as to be more or less disjoint. We therefore did not include the study of Richardson and Wing (1999) because it is largely subsumed in the International Agency for Research on Cancer 15-country study of Vrijheid *et al.* (2007), with minimal extra years of follow-up (to 31/12/1990 for Richardson and Wing (1999), vs 31/12/1984 in Vrijheid *et al.* (2007)) and likewise, we did not include the study of McGeoghegan *et al.* (2008) because the British Nuclear Fuels Limited worker cohort is largely subsumed within the study of Muirhead *et al.* (2009) and has only four more years of follow up (to 31/12/2005 vs 31/12/2001 for Muirhead *et al.* (2009)). However, we tested for the effect of including both these studies in the meta-analysis.

Outcomes included in our analysis had to fall within one of the four major subtypes of circulatory disease determined *a priori*, namely: ischemic heart disease (IHD, ICD10 I20-25); heart disease apart from IHD (ICD10 I26-52); cerebrovascular disease (ICD10 I60-69); and all other circulatory diseases (ICD10 I00-19, I53-59, I70-99). This resulted in the exclusion of the study of Talbott *et al.* (2003) that only assessed heart disease, and so cannot be included within any of these four disease endpoints. For each study we selected disjoint endpoint groups with maximum coverage within these four circulatory disease subtype groups. We used morbidity rather than mortality data from the Mayak worker studies of Azizova *et al.* (2010a; 2010b) because of the significant loss of follow-up for the mortality study and low diagnostic accuracy for death certificate reporting for this cohort.

The results of the Medline and ISI Thompson searches were cross-checked by MPL and WZ. Additional checks were made using ISI Thompson citations of various review articles (Little *et al.* 2008; McGale and Darby 2005) and other sources, as detailed in Little *et al.* (2008). MOOSE guidelines for meta-analysis were used (Stroup *et al.* 2000) [see Supplemental Material, Table S1 for a checklist indicating compliance with MOOSE

guidelines]

A total of 10 studies met our criteria for inclusion. Although the Japanese data (Shimizu et al. 2010; Yamada et al. 2004), and many of the occupational studies included individuals with cumulative absorbed dose ranges > 0.5 Sv, average cumulative whole body doses from external sources of radiation in cohorts included in our analysis were generally < 0.2 Sv [with the exception of the Mayak worker study with an average dose of about 0.8 Gy (Azizova et al. 2010a; Azizova et al. 2010b)], and the occupational cohorts were all exposed at low daily dose rates (generally < 1 mSv/day, and all < 10 mSv/day). Details regarding the quality of dosimetry; assessment of disease endpoints, selection criteria to determine cohort eligibility, circulatory disease risk factors assessed, and statistical analyses used by the 10 studies are provided in Supplemental Material, Table S2.

Statistical Methods for Meta-Analysis

The analytical techniques extend those employed previously (AGIR 2010; Little et al. 2008; Little et al. 2009b; Little et al. 2010) to analyze different data (including studies of medically-exposed populations as well as the studies included in this analysis). Pooled ERR per Sv were estimated for the four circulatory disease subgroups defined above.

In the absence of significant heterogeneity (see below) we computed the best linear unbiased estimate (inverse-variance weighted) of ERR (ERR_{tot}) as:

$$ERR_{tot} = \frac{\sum_{i=1}^N ERR_i / sd(ERR_i)^2}{\sum_{i=1}^N 1 / sd(ERR_i)^2} \quad [1]$$

where ERR_i indicates the ERR reported by the i^{th} study. This estimate has a standard deviation given by:

$$sd(ERR_{tot}) = \frac{1}{\left[\sum_{i=1}^N 1 / sd(ERR_i)^2 \right]^{0.5}} \quad [2]$$

These formulae were used to compute aggregate measures of ERR and their associated 95% confidence intervals [obtained as $ERR_{tot} \pm N_{0.975} \times sd(ERR_{tot})$] in Table 2. [$N_{0.975} \approx 1.96$ is the 97.5% percentile point of the standard normal distribution.] One-sided p -values were computed from the centiles of the normal distribution. Equation (2) is a consistent estimate of the standard deviation. Standard deviations were estimated for the individual studies based on confidence intervals reported in the published papers.

Heterogeneity was assessed via the standard χ^2 statistic and calculated as:

$$\chi^2 = Q = \sum_{i=1}^N [(ERR_i - ERR_{tot}) / sd(ERR_i)]^2 \quad [3]$$

The above estimates correspond to a fixed-effect model, in which $ERR_i \sim N(\mu, \sigma_i^2)$. When heterogeneity is statistically significant (assessed by comparing Q with centiles of the χ^2 distribution with the appropriate number of degrees of freedom = $N - 1$) a random-effects model is more appropriate, in which we assume $ERR_i | \delta_i \sim N(\mu + \delta_i, \sigma_i^2)$ and that $\delta_i \sim N(0, \Delta^2)$. The random-effects model assumes that inference is being made about a hypothetical population of studies of which the observed studies involved are assumed to constitute a “random sample” of potential studies of the same effects. Following DerSimonian and Laird (1986) we compute the 1-step estimate of Δ^2 by equating the statistic Q and its expectation under this model to obtain:

$$\Delta^2 = \max \left[0, \frac{Q - (N - 1)}{\sum_{i=1}^N 1 / sd(ERR_i)^2 - \frac{\sum_{i=1}^N 1 / sd(ERR_i)^4}{\sum_{i=1}^N 1 / sd(ERR_i)^2}} \right] \quad [4]$$

Similarly to the above, we then compute the best linear unbiased estimate (inverse-variance weighted) of ERR, given by:

$$ERR_{tot} = \frac{\sum_{i=1}^N ERR_i / [sd(ERR_i)^2 + \Delta^2]}{\sum_{i=1}^N 1 / [sd(ERR_i)^2 + \Delta^2]} \quad [5]$$

Similarly to the above, this estimate has a standard deviation given by:

$$sd(ERR_{tot}) = \frac{1}{\left[\sum_{i=1}^N 1 / [sd(ERR_i)^2 + \Delta^2] \right]^{0.5}} \quad [6]$$

We estimated 1-sided p -values (assuming only detrimental effects) in the standard way from the mean, μ , and standard deviation, σ , derived from the meta-analysis for each circulatory disease endpoint, as $P[N(0,1) < -\mu/\sigma]$. Statistical significance was defined by $p < 0.05$. The Egger test of publication/selection bias (Egger et al. 1997; Steichen 1998) and the Duval and Tweedie (2000) “trim and fill” method of correction for publication/selection bias were employed, as shown in Supplemental Table S3. All statistical models were fitted using Stata (version Stata/SE 11.2 for Windows (32 bit), 2011).

Estimates of population risks

We used pooled ERR from the meta-analysis to derive population-based excess absolute risk (EAR) estimates according to underlying cause-specific mortality rates for each population. Specifically, we used estimates for the year 2003 in England and Wales (Office for National Statistics 2004), 2009 for Japan (Statistics and Information Department 2011), and the latest available World Health Organization data for China (2000), France (2007), Germany (2006), Russia (2006), Spain (2005), Ukraine (2008), and USA (2005) (World Health Organization 2010). We assumed a 5-year minimum latency period, after which the excess relative risk was assumed to apply for the remainder of life. For all of the countries listed above we estimated the risk of exposure-induced death (REID) per Sv, years of life lost per Sv, and years of life lost per radiation-induced circulatory disease death, by applying methods previously used to derive comparable estimates for radiation-induced cancer (United Nations

Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008). In addition, we obtained population risk estimates for radiation-induced solid cancers (ICD10 C00-C80) and leukemias excluding chronic lymphocytic leukemia (CLL) (ICD10 C91-C95 excluding C91.1) for China, Japan, the UK, and the USA for comparison with population risk estimates for circulatory diseases (UNSCEAR 2008).

RESULTS

Meta-Analysis

A funnel plot shows little evidence of publication or selection bias in the meta-analysis, at least once the very large (but imprecise) ERR in one study (Laurent et al. 2010) are removed (Figure 1). More formally, an Egger test for bias (Egger et al. 1997) reveals no significant evidence for publication or selection bias in any circulatory disease endpoint: Egger test p -values ranged from 0.322 for ischemic heart disease to 0.692 for cerebrovascular disease, and little difference is made to risk coefficients if trim-and-fill publication/selection-bias correction methods are used (Duval and Tweedie 2000) (Supplemental Material, Table S3).

Table 1 demonstrates that most ERR estimates (21 of 29) are positive, and with the exception of the study of Laurent *et al.* (2010) are generally of modest size, with absolute value $< 1 \text{ Sv}^{-1}$. The results of the meta-analysis (Table 2) using a random effects model show a statistically significant ERR per Sv for ischemic heart disease (ERR = 0.10 Sv^{-1} , 95% CI 0.04, 0.15, $p < 0.001$), cerebrovascular disease (stroke) (ERR = 0.21 Sv^{-1} , 95% CI 0.02, 0.39, $p = 0.014$) and circulatory disease other than heart disease and stroke (ERR = 0.19 Sv^{-1} , 95% CI -0.00, 0.38, 1-sided $p = 0.026$). The ERR for other (non-ischemic) heart disease is significant at least for the fixed-effect model (ERR = 0.12 Sv^{-1} , 95% CI -0.01, 0.25, $p = 0.031$), but not for the random effects model (ERR = 0.08 Sv^{-1} , 95% CI -0.12, 0.28, $p = 0.222$) (Table 2). The heterogeneity in ERR between the various studies and endpoints for ischemic and

non-ischemic heart disease is not statistically significant ($p>0.1$), although it is significant for the other endpoints ($p\leq 0.001$; Table 2).

In general, ERR estimates were not particularly sensitive to the removal of individual studies Supplemental Material Table S4, though effects were greater for the endpoints addressed by only a few studies, in particular other (non-ischemic) heart disease (3 studies) and all circulatory disease apart from heart disease and cerebrovascular disease (3 studies). Exclusion of the Mayak workforce studies (Azizova et al. 2010a; Azizova et al. 2010b) had the greatest effect, resulting in a random effect ERR for ischemic heart disease of 0.07 (-0.01, 0.15) compared with 0.10 (0.04, 0.15) and 0.12 (0.02, 0.23) for cerebrovascular disease compared with 0.21 (0.02, 0.39). Addition of the Richardson and Wing (1999) or the McGeoghegan *et al.* (2008) data to the ischemic heart disease category (the only circulatory disease group to which they can contribute) makes very little difference – the fixed effects ERR changes from 0.10 (95% CI 0.05, 0.15) (Table 2) to 0.10 (95% CI 0.06, 0.15) or 0.10 (95% CI 0.05, 0.15), respectively, and the random effects ERR changes from 0.10 (95% CI 0.04, 0.15) (Table 2) to 0.13 (95% CI 0.04, 0.23) or 0.09 (95% CI 0.03, 0.16), respectively.

Population Risks

Population-based excess absolute risk (EAR) estimates for radiation-exposure-induced death (REID) for all circulatory disease range from 2.50% per Sv (95% confidence interval (CI) 0.77 to 4.22) for France to 8.51% per Sv (95% CI 4.00 to 13.02) for Russia, reflecting the underlying risk of circulatory disease mortality (Table 3). Estimated circulatory disease mortality risks are generally dominated (in Germany, Russia, Ukraine, the UK, and the USA) by ischemic heart disease and cerebrovascular disease (Tables 3 and 4). The random effects model, based on aggregate ERR data from individual studies without age at exposure information, predicts that population circulatory disease EAR (REID) in the UK varies minimally with age at exposure (Table 5). However, in this instance more weight should be

attached to models fitted to the current Japanese atomic-bomb survivor mortality data (Shimizu et al. 2010) in Supplemental Material, Tables S5, S6, which has information on variation of risk by age at exposure – risks reduce from 20.73% per Sv at age 9 years or less to 2.05% per Sv at age 70 years or more (Table 5). There are indications of the same direction of trend with age at exposure also in the French nuclear workers (Laurent et al. 2010), although there are no such trends (but apparently little power to assess them) in the IARC study (Vrijheid et al. 2007) (results not shown).

In aggregate, EAR coefficients are similar to those for cancer mortality, and the indications are that, as for cancer, there is a pronounced reduction of risk with increasing age at exposure (Table 5); for example, the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR 2008) estimated that the total cancer REID is in the range 4.16% to 5.58% for China, Japan, the UK and the USA (Table 3). In different terms, the risks for a UK population are 0.146 (95% CI 0.065 to 0.227) years of life lost per Sv and 8.61 years of life lost per radiation-induced death, and 0.162 years of life lost per Sv (95% CI 0.018 to 0.307) and 7.26 years of life lost per radiation-induced death, for ischemic heart disease and cerebrovascular disease (stroke), respectively (Table 4). These years of life lost per radiation-induced death figures are substantially lower than the corresponding ones for solid cancers (13.8 to 14.4) and leukemia (19.8 to 31.6; Table 4), reflecting the fact that circulatory disease mortality tends to occur later in life.

DISCUSSION

We estimated statistically significant excess relative risks for four subtypes of circulatory disease in people exposed to radiation. There was significant heterogeneity among individual study estimates for cerebrovascular disease (stroke) and other circulatory diseases, but not for ischemic and other (non-ischemic) heart disease. These results confirm and extend a previous

analysis that also found statistically significant excess relative risks for ischemic heart disease and cerebrovascular disease (stroke) (AGIR 2010).

Most of the studies considered here involved low to moderate average cumulative radiation doses (0.2 Gy or less), with participants in the occupational studies exposed at near-background dose rates. Nevertheless, the small numbers of participants exposed at high cumulative doses (0.5 Gy or above) drive the observed trends in most cohorts with these higher dose groups (see Table 1).

Population-based EAR estimates for circulatory disease mortality were dominated by estimated risks for ischemic heart disease and cerebrovascular disease (stroke), which is unsurprising, given that deaths from these two endpoints account for the largest number of deaths from circulatory disease and that the excess risk is a simple multiple of the underlying circulatory disease risk.

A critical question in these calculations is whether the risk coefficients derived here are applicable to the lower cumulative doses (<100 mSv) or low dose-rates (<5 mSv/h) of principal relevance to radiological protection. We fitted a linear excess relative risk model to the data in the meta-analysis, so we implicitly assumed a linear association of risk at low doses and dose rates. There is little evidence for nonlinearity in the dose-response curve for circulatory disease in Japanese atomic-bomb survivors (Shimizu et al. 2010; Yamada et al. 2004) or in the Mayak workers (Azizova et al. 2010a; Azizova et al. 2010b), so this assumption seems reasonable in the current analysis. At least for ischemic and non-ischemic heart disease, additional support for a linear relationship between risk and low doses or low dose rates can be derived from the consistency of ERR per Sv between Japanese atomic-bomb survivors with moderate radiation doses at high dose rates (Shimizu et al. 2010; Yamada et al. 2004) and occupational cohorts with protracted exposures. Currently, an etiologic mechanism for associations between low-level radiation and circulatory disease risk

is unclear, so there are no sound biological grounds on which to base selection of a model for extrapolating the risks to low doses or low dose-rates (AGIR 2010). However, a candidate mechanism, based on monocyte cell killing in the intima, suggests that circulatory disease risks would be approximately proportional to dose at low dose rates (Little et al. 2009a), but, because of saturation of repair systems, effects would be greater for exposures to higher doses and dose rates (UNSCEAR 1993). Although this mechanism is consistent with the occupational data, it is speculative, and not yet experimentally confirmed. Epidemiological data suggest that circulatory disease risk is significantly elevated only for acute or cumulative doses of about 0.5 Gy and above; nonetheless, the dose-rate independence of risk remains (AGIR 2010).

All studies included in the meta-analysis were either of the Japanese atomic-bomb survivors or of occupationally exposed groups. All occupational groups are to some extent selected, from populations that are sufficiently fit to be employed as radiation workers. The degree of selection (as a result of mortality in the period from the bombings in August 1945 to the assembly of the cohort in October 195) in the Japanese atomic-bomb survivor cohort has long been controversial (Little and Charles 1990; Stewart and Kneale 1984). There is evidence of selection in at least the earlier years of follow-up for some non-cancer endpoints (Ozasa et al. 2012; Preston et al. 2003). As risks in a general unselected population are likely to be higher than in a selected one, it is possible that the risks given here are underestimates of those that are applicable to a general population; they are more likely to be correct for occupationally-exposed groups subject to a similar degree of healthy-worker selection as those considered here.

We estimated excess relative risk, the metric used in most published data (AGIR 2010). Accordingly, for the population risk estimates, we assumed a relative risk model for projecting risk to the end of life, starting 5 years after exposure. Excess relative risk does not

substantially vary by sex, time since exposure, or age at exposure in Japanese atomic-bomb survivors (Little 2004; Preston et al. 2003), although increasing time since exposure trends have been observed in other groups (Vrijheid et al. 2007). Implicitly, we also assumed that excess relative risk is invariant across populations. This assumption may be reasonable for ischemic and other (non-ischemic) heart disease ERRs, which did not show statistically significant heterogeneity across exposed populations (Japanese atomic-bomb survivors and largely European/American occupational data), but this assumption may not be appropriate for the other circulatory disease subgroups, where heterogeneity was significant.

Candidate biological mechanisms for effects of radiation on circulatory disease have been recently reviewed (AGIR 2010; Little et al. 2008; Schultz-Hector and Trott 2007). At high radiotherapeutic doses (>5 Gy), the cell-killing effect on capillaries and endothelial cells plausibly explains effects on the heart and other parts of the circulatory system (Schultz-Hector and Trott 2007). At lower doses (0.5 – 5 Gy), in humans and in *in vivo* and *in vitro* experiments, many inflammatory markers are upregulated long after exposure to radiation, although for exposures less than about 0.5 Gy, the balance shifts toward anti-inflammatory effects (Little et al. 2008; Mitchel et al. 2011), implying that the initiating mechanisms for adverse effects in this dose range would not directly result from inflammation. A recent analysis of renal failure mortality in the atomic-bomb survivors suggests that radiation-induced renal dysfunction may be a factor in causing increased circulatory disease (Adams et al. 2012).

The generally uniform whole-body, low linear energy transfer radiation in the cohorts we analysed is uninformative as to specific target tissues. What the target tissues are for circulatory system effects at moderate and low doses (<0.5 Gy) remains uncertain. Dose-related variations in T-cell and B-cell populations in Japanese atomic-bomb survivors suggest that the immune system may be adversely affected (Kusunoki et al. 1998). Together with the

known involvement of the immune system in cardiovascular disease (Danesh et al. 2002; Ridker 1998; Whincup et al. 2000), these results suggest that whole-body or bone-marrow dose might be the most relevant to radiation effects. A mechanism based on monocyte cell killing in the arterial intima suggests that the target for atherosclerosis is the arterial intima (Little et al. 2009a); however, as noted above, this mechanism remains speculative.

In their reviews, Little et al. (2008; 2010) document abundant radiobiological reasons for considering studies of moderate and low doses separately from studies of high (i.e., radiotherapeutic) doses because mechanisms of effect are likely to differ. That said, the risks observed in radiotherapeutic studies (Supplemental Material, Table S7) are not inconsistent with those in the lower-dose studies that are the focus of this paper and suggest common mechanisms over this dose range. However, given the modest level of excess risk at these lower doses, and the many lifestyle factors that can affect the risk of circulatory disease, attributing causation to the observed associations requires caution. Interpreting the results of studies in which there is no, or at best limited, lifestyle information, that is to say in studies apart from the Japanese atomic-bomb survivors (Shimizu et al. 2010; Yamada et al. 2004) and the Mayak nuclear workers (Azizova et al. 2010a; Azizova et al. 2010b), would be particularly speculative.

The substantial and statistically significant heterogeneity in the estimated relative risks of circulatory disease other than heart disease among the studies considered is not surprising given variation in the distributions of different risk factors across populations, but it limits interpretation of the observed associations for these endpoints. Epidemiological research has identified specific risk factors for circulatory disease, including male sex, family history of heart disease, cigarette smoking, diabetes, high blood pressure, obesity, increased low-density lipoprotein cholesterol, and decreased high-density lipoprotein cholesterol plasma levels (Burns 2003; Wilson et al. 1998). Lifestyle factors (in particular shift work in occupational

groups) (Tüchsen et al. 2006) and infections (Danesh et al. 2002; Ridker 1998; Whincup et al. 2000) are also potential risk factors for circulatory disease. We could not correct for any of these variables in our meta-analysis. Statistical methods (i.e., random effects models) are available to accommodate heterogeneity (DerSimonian and Laird 1986), but these methods may not adequately account for the variation induced by confounding or effect modification. The interactions of these risk factors with possible radiation effects are unknown, but confounding or effect modification cannot be ruled out in studies in which no adjustment was made; in the two cohorts where it was possible to make adjustment for such risk factors little difference was made to radiation risk (Azizova et al. 2010a; Azizova et al. 2010b; Shimizu et al. 2010).

A potential problem in meta-analyses is publication bias, which selects against studies that do not produce significant findings, potentially biasing pooled estimates upwards, or selection bias on the part of those selecting the cohorts from the database searches, which could be either positive or negative. We believe that publication bias is unlikely because radiation-induced cardiovascular disease has been an issue in the Japanese atomic-bomb survivor data for at least 15 years (Preston et al. 2003; Shimizu et al. 1992; Wong et al. 1993); as such negative findings are likely to be of sufficient interest to be published, and therefore this should not greatly affect the findings of our meta-analysis, concentrating as it does on results published since 1990. There is little internal evidence of either publication or selection bias (Figure 1, Supplemental Material, Table S3), although at least for the endpoints of other (non-ischemic) heart disease and all other circulatory disease the Egger test has little power. The fact that the two persons (MPL, WZ) evaluating the database search agreed on the included studies also suggests that selection bias is minimal.

We chose to limit our results to studies published as full papers and referenced in Medline or ISI Thompson. We judge that the most important and high quality studies are

likely to be published as full papers. All of the studies selected were cohort studies (although this was not a criterion for being chosen), and all had reasonable quality dosimetry (see Supplemental Material, Table S2). Only two of the studies, those of the Japanese atomic-bomb survivors (Shimizu et al. 2010) and Mayak workers (Azizova et al. 2010a; Azizova et al. 2010b) had information on lifestyle factors, in particular cigarette smoking, drinking and other variables associated with circulatory disease. The lack of evidence of strong positive associations between various non-malignant smoking-related respiratory diseases and dose in various worker studies (Laurent et al. 2010; Muirhead et al. 2009; Vrijheid et al. 2007) suggests that cigarette smoking is unlikely to have been an important positive confounder of the association with circulatory disease in these groups, and that bias will therefore be if anything towards the null. Information on socioeconomic status (industrial versus non-industrial, educational level) in various worker studies (Laurent et al. 2010; McGeoghegan et al. 2008; Muirhead et al. 2009; Vrijheid et al. 2007) provides only partial control for confounding by lifestyle/environmental risk factors.

Although we eliminated studies with a large degree of overlap, some degree of overlap remained among studies included in the meta-analysis, particularly for the morbidity and mortality data for the Japanese atomic-bomb survivors (Shimizu et al. 2010; Yamada et al. 2004). However, the largest component of circulatory disease morbidity, hypertension (about half the total number of cases), has a much lower ERR, 0.05 Sv^{-1} (Yamada et al. 2004), than either cerebrovascular disease (stroke), 0.12 Sv^{-1} , or heart disease, 0.18 Sv^{-1} , mortality (Shimizu et al. 2010), suggesting that the overlap may not be large. There is also likely to be statistical dependence between the risks of some endpoints within the atomic-bomb survivor morbidity study (Yamada et al. 2004) although in the most likely overlapping categories (hypertension, hypertensive heart disease, cerebrovascular disease (stroke)) the numbers involved are relatively modest. The effect of removing the morbidity study (Yamada et al.

2004) from the analysis (Supplemental Material, Table S4) is generally to slightly increase risks; there is a more substantial elevation for circulatory disease apart from heart disease and cerebrovascular disease, but this contributes relatively modestly (6-25%) to overall circulatory disease mortality (Table 3). There is overlap between the UK worker study (Muirhead et al. 2009) and the 15-country worker study (Vrijheid et al. 2007), but this is probably not substantial, since the former has 9 more years of follow-up (1993-2001) and the latter includes data from 14 countries in addition to the UK.

Some of the heterogeneity that we observed in relation to circulatory disease apart from heart disease is driven by morbidity versus mortality differences, reinforcing previous findings (Little et al. 2010). Although one can argue that relative risks should not be different for mortality and morbidity (although absolute risks very well could be), the varying definitions and ascertainment of morbidity endpoints mean that different degrees of severity of circulatory disease are being encompassed. The relative risks of mortality data should be more similar (than mortality vs. morbidity)(Little et al. 2010), although the uncertainty from misclassification remains and varies over time. Both outcome and exposure misclassification would be expected to bias results towards the null in most cases, unless the bias was differential (e.g., outcome misclassification associated with exposure) (Copeland et al. 1977). We use morbidity and mortality data in the Japanese atomic-bomb survivors, which contribute to some extent independently (as discussed above) and are of similar quality (Shimizu et al. 2010; Yamada et al. 2004). However, we use morbidity rather than mortality data in the Mayak worker studies (Azizova et al. 2010a; Azizova et al. 2010b) because of the significant problems with loss of follow-up in the mortality data (as soon as workers moved out of the closed cities in the ex-USSR), and the much lower diagnostic accuracy in this cohort of death certificate reporting.

In the Japanese atomic-bomb survivors, respiratory and digestive diseases were also

elevated (Preston et al. 2003), implying a lack of specificity of risk in this cohort. However, there is no evidence of excess risk for any non-malignant diseases apart from circulatory disease in the other cohorts considered here (Laurent et al. 2010; Muirhead et al. 2009; Vrijheid et al. 2007).

In conclusion, our meta-analysis supports an association between low doses and low dose rates of ionizing radiation and an excess risk of ischemic heart disease. For non-ischemic heart disease the association is statistically significant, when using (as is justifiable, given the homogeneity of risk) a fixed-effect model. The association is less certain for other circulatory diseases given the heterogeneity in these endpoints among the studies. The evidence presented here indicates a need to conduct more detailed epidemiological studies that are capable of addressing potential confounding and misclassifying factors and possible selection bias that could influence these results, and in particular the need for a better understanding of biological mechanisms that might be responsible for the association. The estimates of population-based excess mortality risks for circulatory disease are similar to those for radiation-induced cancer, as also noted previously in relation to non-cancer disease (Preston et al. 2003). If associations between low-level exposure to radiation and circulatory diseases reflect an underlying causal relationship that is linear at low doses, then the overall excess risk of mortality after exposure to low doses or low dose-rates of radiation may be about twice that currently assumed based on estimated risks of mortality due to radiation-induced cancers alone.

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Table 1. Estimated Excess Relative Risks of Circulatory Disease in the Japanese Atomic-bomb Survivors and Occupational and

Environmental Exposure Studies. (Adapted from Little et al. (2008; 2010)). All data are in relation to underlying cause of death, unless otherwise indicated.

Data	Reference	Average heart/brain dose (range) (Sv)	Numbers in cohort (person years follow-up)	Endpoint (mortality unless otherwise indicated)	Excess relative risk Sv ⁻¹ (and 95% CI)
Japanese atomic-bomb survivors					
Mortality	Shimizu et al. 2010	0.1 (0 - 4) ^a	86,611 (n.a.)	Ischemic heart disease (ICD9 410-414)	0.02 (-0.10, 0.15)
				Rheumatic heart disease (ICD9 393-398)	0.86 (0.25, 1.72)
				Heart failure (ICD9 428)	0.22 (0.07, 0.39)
				Other heart disease (ICD9 390-392, 415-427, 429)	-0.01 (-0.21, 0.24)
				Cerebrovascular disease (stroke) total (ICD9 430-438) ^b	0.12 (0.05, 0.19) ^b
				Circulatory disease apart from heart disease and stroke (ICD9 390-392, 401, 403, 405, 439-459) ^b	0.58 (0.45, 0.72) ^b
Morbidity	Yamada et al. 2004	0.1 (0 - 4) ^c	10,339 (n.a.)	Hypertension incidence, 1958-1998 (ICD9 401)	0.05 (-0.01, 0.10) ^c
				Hypertensive heart disease incidence, 1958-1998 (ICD9 402, 404)	-0.01 (-0.09, 0.09) ^c
				Ischemic heart disease incidence, 1958-1998 (ICD9 410-414)	0.05 (-0.05, 0.16) ^c
				Aortic aneurysm incidence, 1958-1998 (ICD9 441, 442)	0.02 (-0.22, 0.41) ^c
				Cerebrovascular disease (stroke) incidence, 1958-1998 (ICD9 430, 431, 433, 434, 436)	0.07 (-0.08, 0.24) ^c
Occupational studies					
Mayak workers	Azizova et al. 2010a; 2010b	0.83 (0 - 5.92) ^d	12,210 (205,249)	Ischemic heart disease morbidity (ICD9 410-414)	0.119 (0.051, 0.186) ^{d, e}
			12,210 (249,530)	Cerebrovascular disease (stroke) morbidity (ICD9 430-432, 434, 436)	0.449 (0.338, 0.559) ^{d, e}

Table 1 (continued)

Data	Reference	Average heart/brain dose (range) (Sv)	Numbers in cohort (person years follow-up)	Endpoint (mortality unless otherwise indicated)	Excess relative risk Sv ⁻¹ (and 95% CI)
Chernobyl emergency workers	Ivanov et al. 2006	0.109 (0 - >0.5)	61,017 (n.a.)	Hypertension (ICD10 I10-I15) morbidity	0.26 (-0.04, 0.56)
				Ischemic heart disease (ICD10 I20-I25) morbidity	0.41 (0.05, 0.78)
				Other heart disease (ICD10 I30-I52) morbidity	-0.26 (-0.81, 0.28)
				Cerebrovascular disease (stroke) (ICD10 I60-I69) morbidity	0.45 (0.11, 0.80)
				Morbidity from diseases of arteries, arterioles and capillaries (ICD10 I70-I79)	0.47 (-0.15, 1.09)
				Morbidity from diseases of veins, lymphatic vessels and lymph nodes (ICD10 I80-I89)	-0.26 (-0.70, 0.18)
German uranium miner study	Kreuzer et al. 2006	0.041 (0 – 0.909) ^d	59,001 (1,801,626)	Cerebrovascular disease (stroke) (ICD10 I60-I69)	0.09 (-0.6, 0.8) ^d
EdF workers	Laurent et al. 2010	0.0215 (0 – 0.6)	22,393 (440,984)	Ischemic heart disease	4.1 (-2.9, 13.7) ^f
				Cerebrovascular disease (stroke)	17.4 (0.2, 43.9) ^f
Eldorado uranium miners and processing (male) workers	Lane et al. 2010	0.0522 (<0.0234 – >0.1215)	16,236 (508,673)	Ischemic heart disease	0.15 (-0.14, 0.58)
				Cerebrovascular disease (stroke)	-0.29 (<-0.29, 0.27)
3 rd Analysis of UK National Registry for Radiation Workers	Muirhead et al. (2009)	0.0249 (<0.01 - >0.4)	174,541 (3.9 x 10 ⁶)	Ischemic heart disease (ICD9 410-414)	0.259 (-0.05, 0.61)
				Cerebrovascular disease (stroke) (ICD9 430-438)	0.161 (-0.42, 0.91)
IARC 15-country nuclear worker study	Vrijheid et al. (2007)	0.0207 (0.0 - >0.5)	275,312 (4,067,861)	Ischemic heart disease (ICD10 I20-I25)	-0.01 (-0.59, 0.69)
				Heart failure (ICD10 I50)	-0.03 (<0, 4.91)
				Cerebrovascular disease (stroke) (ICD10 I60-I69)	0.88 (-0.67, 3.16)

^aAnalysis based on colon dose. ^bAnalysis using underlying or contributing cause of death. ^cAnalysis based on stomach dose, derived from Table 3 of Yamada et al. (2004) with smoking and drinking in the stratification. ^dRisk estimates in relation to cumulative whole body external gamma dose. ^eAssuming a lag period of 10 years. ^f90% CI. ^gEstimate derived from log-linear model, evaluated at 1 Sv.

Table 2. Excess Relative Risk Coefficients for Circulatory Diseases as a Result of Exposure to Low-Level Radiation at least 5 Years Earlier, by Disease. Values are from Table 1, unless otherwise indicated

Disease (ICD Code)	Studies Included	Fixed-effect estimate of ERR per Sv (95% CI)	Random-effect estimate of ERR per Sv (95% CI)	1-sided significance, <i>P</i> (fixed effect / random effect)	Heterogeneity χ^2 (df) / <i>P</i>
Ischemic heart disease (ICD10 I20-I25)	Yamada et al. 2004, Ivanov et al. 2006, Vrijheid et al. 2007, Muirhead et al. 2009, Azizova et al. 2010a ^a , Shimizu et al. 2010, Laurent et al. 2010, Lane et al. 2010	0.10 (0.05 to 0.15)	0.10 (0.04 to 0.15)	<0.001 / <0.001	7.20 (7) / 0.408
Other (non-ischemic) heart disease (ICD10 I26-I52)	Ivanov et al. 2006, Vrijheid et al. 2007 ^b , Shimizu et al. 2010 ^c	0.12 (-0.01 to 0.25)	0.08 (-0.12 to 0.28)	0.031 / 0.222	4.65 (3) / 0.199
Cerebrovascular disease (stroke) (ICD10 I60-I69)	Yamada et al. 2004, Ivanov et al. 2006, Kreuzer et al. 2006, Vrijheid et al. 2007, Azizova et al. 2010b ^d , Muirhead et al. 2009, Shimizu et al. 2010, Laurent et al. 2010, Lane et al. 2010	0.20 (0.14 to 0.25)	0.21 (0.02 to 0.39)	<0.001 / 0.014	34.28 (8) / <0.001
Circulatory disease apart from heart disease and stroke (ICD10 I00-I19, I53-I59, I70-I99)	Yamada et al. 2004 ^e , Ivanov et al. 2006 ^f , Shimizu et al. 2010 ^g	0.10 (0.05 to 0.14)	0.19 (-0.00 to 0.38)	<0.001 / 0.026	66.83 (7) / <0.001

^aAnalysis based on morbidity from ischemic heart disease, with a 10-year lag.

^bAnalysis based on mortality from heart failure.

^cAnalysis based on mortality from heart failure and other heart disease.

^dAnalysis based on morbidity from cerebrovascular disease, with a 10-year lag.

^eAnalysis based on morbidity from hypertension, hypertensive heart disease and aortic aneurysm.

^fAnalysis based on morbidity from hypertension, disease of arteries, arterioles and capillaries, veins, lymphatic vessels and lymph nodes.

^gAnalysis based on mortality from rheumatic heart disease and circulatory disease apart from heart disease and cerebrovascular disease.

Table 3. Estimated Excess Risk of Radiation-Exposure-Induced Death for Various Subtypes of Circulatory Disease, by Country. All calculations assume a single acutely delivered test dose of 0.01 Sv, and are calculated assuming a random-effects model.

Country (year at which underlying mortality rates were determined)	Baseline proportion of deaths due to circulatory disease	Radiation-Exposure-Induced Death, x 10 ⁻² Sv (95% CI)						UNSCEAR risks (UNSCEAR 2008)	
		Ischemic heart disease (ICD10 I20-I25) ^a	Other (non-ischemic) heart disease (ICD10 I26-I52) ^b	Cerebrovascular disease (stroke) (ICD10 I60-I69) ^c	Other circulatory disease (ICD10 I00-I19, I53-I59, I70-I99) ^d	All circulatory disease (ICD10 I00-I99) ^e	All solid cancer (ICD10 C00-C80)	Leukemia excluding CLL (ICD10 C91-C95 – C91.1)	
China (2000)	42.1%	0.92 (0.41, 1.42)	0.11 (-0.16, 0.37)	4.31 (0.48, 8.14)	1.43 (-0.01, 2.86)	6.76 (2.63, 10.89)	3.95 ^f 3.89 ^g	0.27 ^h 0.42 ⁱ	
France (2007)	20.8%	0.50 (0.22, 0.78)	0.54 (-0.85, 1.94)	0.92 (0.10, 1.74)	0.53 (0.00, 1.05)	2.50 (0.77, 4.22)	-	-	
Germany (2006)	48.7%	1.71 (0.76, 2.65)	0.97 (-1.52, 3.46)	1.69 (0.19, 3.19)	1.38 (-0.01, 2.76)	5.75 (2.39, 9.10)	-	-	
Japan (2009)	31.1%	0.57 (0.25, 0.88)	0.80 (-1.25, 2.85)	2.19 (0.24, 4.14)	0.45 (0.00, 0.91)	4.01 (1.13, 6.89)	4.65 ^f 4.90 ^g	0.32 ^h 0.43 ⁱ	
Russia (2006)	64.4%	2.82 (1.26, 4.39)	0.31 (-0.49, 1.11)	4.59 (0.51, 8.66)	0.79 (0.00, 1.57)	8.51 (4.00, 13.02)	-	-	
Spain (2005)	35.8%	0.91 (0.41, 1.42)	0.82 (-1.28, 2.52)	1.91 (0.21, 3.60)	0.81 (0.00, 1.63)	4.45 (1.73, 7.17)			

Table 3 (continued)

Country (year at which underlying mortality rates were determined)	Baseline proportion of deaths due to circulatory disease	Radiation-Exposure-Induced Death, x 10 ⁻² Sv (95% CI)						UNSCEAR risks (UNSCEAR 2008)	
		Ischemic heart disease (ICD10 I20-I25) ^a	Other (non-ischemic) heart disease (ICD10 I26-I52) ^b	Cerebrovascular disease (stroke) (ICD10 I60-I69) ^c	Other circulatory disease (ICD10 I00-I19, I53-I59, I70-I99) ^d	All circulatory disease (ICD10 I00-I99) ^e	All solid cancer (ICD10 C00-C80)	Leukemia excluding CLL (ICD10 C91-C95 – C91.1)	
Ukraine (2008)	69.2%	4.14 (1.85, 6.43)	0.20 (-0.31, 0.70)	2.85 (0.31, 5.39)	0.93 (0.00, 1.85)	8.11 (4.53, 11.69)			
UK (2003)	39.9%	1.70 (0.76, 2.64)	0.37 (-0.58, 1.32)	2.24 (0.25, 4.22)	0.76 (0.00, 1.53)	5.07 (2.55, 7.58)	5.15 ^f 4.40 ^g	0.38 ^h 0.43 ⁱ	
USA (2005)	39.3%	1.82 (0.81, 2.82)	0.57 (-0.89, 2.03)	1.29 (0.14, 2.44)	0.80 (0.00, 1.61)	4.48 (2.22, 6.74)	4.74 ^f 4.41 ^g	0.47 ^h 0.42 ⁱ	

^ausing ischemic heart disease relative risk coefficient from Table 2.

^busing non-ischemic heart disease relative risk coefficient from Table 2.

^cusing cerebrovascular disease relative risk coefficient from Table 2.

^dusing all circulatory disease apart from heart disease and cerebrovascular disease relative risk coefficient from Table 2.

^eobtained by summing the risks from component disease categories (ischemic heart, non-ischemic heart, cerebrovascular disease and other circulatory).

^frelative risk model with linear-quadratic dose response, adjusted for sex, age and years since exposure.

^gadditive risk model with linear-quadratic dose response, adjusted for age and years since exposure.

^hrelative risk model with linear-quadratic dose response, adjusted for age.

ⁱadditive risk model with linear-quadratic dose response, adjusted for sex and years since exposure.

Table 4. Estimated Population Mortality Risks for Subtypes of Circulatory Disease and Cancer in the United Kingdom. All calculations assume a single acutely delivered test dose of 0.01 Sv, and are calculated assuming a random-effects model.

Disease	Radiation-exposure-induced deaths, x 10 ⁻² per Sv (95% CI)	Years of life lost per Sv (95% CI)	Years of life lost per radiation-induced death (95% CI)
Ischemic heart disease (ICD10 I20-I25) ^a	1.70 (0.76 to 2.64)	0.146 (0.065 to 0.227)	8.61 (8.61 to 8.61)
Other (non-ischemic) heart disease (ICD10 I26-I52) ^b	0.37 (-0.58 to 1.32)	0.027 (-0.043 to 0.097)	7.36 (7.36 to 7.36)
Cerebrovascular disease (stroke) (ICD10 I60-I69) ^c	2.24 (0.25 to 4.22)	0.162 (0.018 to 0.307)	7.26 (7.26 to 7.26)
Other circulatory disease (ICD10 I00-I19, I53-I59, I70-I99) ^d	0.76 (0.00 to 1.53)	0.065 (0.000 to 0.130)	8.50 (8.50 to 8.50)
All circulatory disease (ICD10 I00-I99) ^e	5.07 (2.55 to 7.58)	0.400 (0.209 to 0.591)	7.90 (7.90 to 7.90)
Solid cancer ^f	5.15	0.711	13.8
Solid cancer ^g	4.40	0.632	14.4
Leukemia ^h	0.38	0.075	19.8
Leukemia ⁱ	0.43	0.135	31.6

^ausing ischemic heart disease relative risk coefficient from Table 2.

^busing non-ischemic heart disease relative risk coefficient from Table 2.

^cusing cerebrovascular disease relative risk coefficient from Table 2.

^dusing all circulatory disease apart from heart disease and cerebrovascular disease relative risk coefficient from Table 2.

^eobtained by summing the risks from component disease categories (ischemic heart, non-ischemic heart, cerebrovascular disease and other circulatory).

^frelative risk model with linear-quadratic dose response, adjusted for sex, age and years since exposure (taken from UNSCEAR 2008).

^gadditive risk model with linear-quadratic dose response, adjusted for age and years since exposure (taken from UNSCEAR 2008).

^hrelative risk model with linear-quadratic dose response, adjusted for age (taken from UNSCEAR 2008).

ⁱadditive risk model with linear-quadratic dose response, adjusted for sex and years since exposure (taken from UNSCEAR 2008).

Table 5. Variation of Population Mortality Risks of Circulatory Disease and Cancer with Age at Exposure in the United Kingdom. All calculations assume a single acutely delivered test dose of 0.01 Sv (unless otherwise indicated), and are calculated assuming a random-effects model. The Life Span Study (LSS) predictions given in columns 2, 3 are based on the optimal model (model 5) fitted to the data of Shimizu et al. (2010) shown in Supplemental Material, Table S6.

Age at Exposure, years	Circulatory disease				Cancer (UNSCEAR 2008)			
	LSS model with adjustment for age at exposure		Meta-analysis without adjustment for age at exposure		Solid cancer		Leukemia	
	Radiation-exposure-induced deaths x 10 ⁻² per Sv	Years of life lost per Sv	Radiation-exposure-induced deaths x 10 ⁻² per Sv (95% CI) ^a	Years of life lost per Sv (95% CI) ^a	Radiation-exposure-induced deaths x 10 ⁻² per Sv	Years of life lost per Sv	Radiation-exposure-induced deaths x 10 ⁻² per Sv	Years of life lost per Sv
0-9	20.73	1.836	5.25 (2.67 to 7.83)	0.459 (0.242 to 0.676)	11.07 ^{b c} 8.36 ^{c d}	1.798 ^{b c} 1.412 ^{c d}	0.74 ^{c e} 0.70 ^{c f}	0.270 ^{c e} 0.335 ^{c f}
10-19	14.18	1.260	5.26 (2.68 to 7.84)	0.459 (0.242 to 0.676)	9.19 ^{b c} 7.39 ^{c d}	1.371 ^{b c} 1.199 ^{c d}	0.52 ^{c e} 0.65 ^{c f}	0.118 ^{c e} 0.269 ^{c f}
20-29	10.09	0.898	5.27 (2.69 to 7.86)	0.458 (0.242 to 0.674)	7.45 ^{b c} 6.34 ^{c d}	1.042 ^{b c} 0.966 ^{c d}	0.46 ^{c e} 0.59 ^{c f}	0.080 ^{c e} 0.208 ^{c f}
30-39	7.48	0.661	5.29 (2.69 to 7.89)	0.453 (0.240 to 0.667)	5.77 ^{b c} 5.20 ^{c d}	0.742 ^{b c} 0.722 ^{c d}	0.43 ^{c e} 0.53 ^{c f}	0.065 ^{c e} 0.153 ^{c f}
40-49	5.75	0.494	5.30 (2.70 to 7.90)	0.439 (0.232 to 0.646)	4.15 ^{b c} 4.01 ^{c d}	0.475 ^{b c} 0.486 ^{c d}	0.40 ^{c e} 0.46 ^{c f}	0.053 ^{c e} 0.105 ^{c f}
50-59	4.53	0.364	5.30 (2.68 to 7.91)	0.410 (0.215 to 0.606)	2.68 ^{b c} 2.83 ^{c d}	0.259 ^{b c} 0.284 ^{c d}	0.37 ^{c e} 0.38 ^{c f}	0.042 ^{c e} 0.065 ^{c f}

Table 5 (continued)

Age at Exposure, years	Circulatory disease				Cancer (UNSCEAR 2008)			
	LSS model with adjustment for age at exposure		Meta-analysis without adjustment for age at exposure		Solid cancer		Leukemia	
	Radiation-exposure-induced deaths x 10 ⁻² per Sv	Years of life lost per Sv	Radiation-exposure-induced deaths x 10 ⁻² per Sv (95% CI) ^a	Years of life lost per Sv (95% CI) ^a	Radiation-exposure-induced deaths x 10 ⁻² per Sv	Years of life lost per Sv	Radiation-exposure-induced deaths x 10 ⁻² per Sv	Years of life lost per Sv
60-69	3.57	0.249	5.19 (2.59 to 7.80)	0.355 (0.181 to 0.528)	1.48 ^{b c} 1.75 ^{c d}	0.113 ^{b c} 0.136 ^{c d}	0.31 ^{c e} 0.29 ^{c f}	0.029 ^{c e} 0.035 ^{c f}
70+	2.05	0.107	3.90 (1.83 to 5.96)	0.200 (0.095 to 0.305)	0.45 ^{b c} 0.66 ^{c d}	0.025 ^{b c} 0.036 ^{c d}	0.17 ^{c e} 0.16 ^{c f}	0.011 ^{c e} 0.011 ^{c f}
All age	8.53	0.732	5.07 (2.55 to 7.58)	0.400 (0.209 to 0.591)	5.15 ^b 4.40 ^d	0.711 ^b 0.632 ^d	0.38 ^e 0.43 ^f	0.075 ^e 0.135 ^f

^aobtained by summing the risks from component disease categories (ischemic heart, non-ischemic heart, cerebrovascular disease and other circulatory).

^brelative risk model with linear-quadratic dose response, adjusted for sex, age and years since exposure.

^csingle acutely delivered test dose of 0.1 Sv.

^dadditive risk model with linear-quadratic dose response, adjusted for age and years since exposure.

^erelative risk model with linear-quadratic dose response, adjusted for age.

^fadditive risk model with linear-quadratic dose response, adjusted for sex and years since exposure.

Figure legend

Figure 1. Funnel plot of excess relative risk (ERR) Sv^{-1} vs standard error of ERR. Each circulatory disease endpoint comprising each of the four main circulatory disease subtypes (ischemic heart disease, other (non-ischemic) heart disease, cerebrovascular disease (stroke), all circulatory disease apart from heart disease and stroke) for each study considered in the meta-analysis (see Table 2) is plotted separately. The red line shows the aggregate random effects excess relative risk estimate. The lower plot shows the data excluding the study of Laurent et al. (2010)

