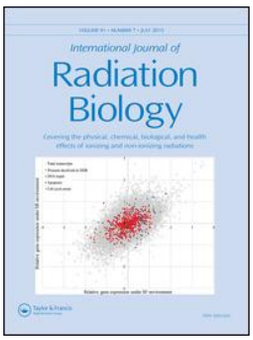


International Journal of Radiation Biology

ISSN: 0955-3002 (Print) 1362-3095 (Online) Journal homepage: http://www.tandfonline.com/loi/irab20

Risk of Solid Cancer in Low Dose-Rate Radiation Epidemiological Studies and the Dose-Rate Effectiveness Factor

Roy Shore, Linda Walsh, Tamara Azizova & Werner Rühm

To cite this article: Roy Shore, Linda Walsh, Tamara Azizova & Werner Rühm (2017): Risk of Solid Cancer in Low Dose-Rate Radiation Epidemiological Studies and the Dose-Rate Effectiveness Factor, International Journal of Radiation Biology, DOI: 10.1080/09553002.2017.1319090

To link to this article: http://dx.doi.org/10.1080/09553002.2017.1319090

Accepted author version posted online: 19 Apr 2017.

Risk of Solid Cancer in Low Dose-Rate Radiation Epidemiological Studies and the Dose-Rate Effectiveness Factor

Roy Shore[1,a], Linda Walsh[2], Tamara Azizova[3] and Werner Rühm[4]

[1] *Radiation Effects Research Foundation, Hiroshima, Japan (Retired), hrshore@gmail.com*

[2] *Department of Physics, University of Zurich, Zurich, Switzerland, linda.walsh@uzh.ch*

[3] *Clinical Department, Southern Urals Biophysics Institute, Ozyorsk, Russia, clinic@subi.su*

[4] *Institute of Radiation Protection, Department of Radiation Sciences, Helmholtz Centre Munich, Neuherberg, Germany, werner.ruehm@helmholtz-muenchen.de*

Prof. Roy Shore, 550 Trails End, Easton PA 18040, USA, hrshore@gmail.com

Roy Shore: PhD (psychology) and DrPH (epidemiology); Professor Emeritus, New York University School of Medicine, New York City, USA; Former Chief of Research, Radiation Effects Research Foundation, Hiroshima, Japan (retired); Past Member of ICRP (Committee 1) and US National Academy of Sciences committees; Member Emeritus, US NCRP

Linda Walsh: UK higher doctorate (DSc) in radiation epidemiology and a PhD in physics; Freelance consultant for radiation epidemiology and data analysis in radiation biology, Munich, Germany; Affiliation: Medical physics, University of Zurich, Switzerland

Tamara Azizova: MD (therapy and neurology) and PhD (radiobiology and neurology); Head, Clinical Department, Southern Urals Biophysics Institute, Ozyorsk, Russia; Conducts studies of cancer, non-cancer diseases and radiation biological mechanisms in Mayak PA workers; Member of ICRP (Committee 1)

Werner Rühm: PhD (Physics), Habilitation (Radiation Biology); Prof. at Ludwig Maximilians University Munich, Faculty of Medicine, Germany; Director (acting), Institute of Radiation Protection, Helmholtz Center Munich, Germany; Chair, ICRP Committee 1 "Radiation Effects"; Chair, EURADOS (European Radiation Dosimetry Group); Editor-in-Chief, Radiation and Environmental Biophysics

Running Title: Dose Rate Effectiveness Factor: epidemiologic findings

Word count: 8,804

Purpose: Estimated radiation risks used for radiation protection purposes have been based primarily on the Life Span Study (LSS) of atomic bomb survivors who received brief exposures at high dose rates, many with high doses. Information is needed regarding radiation risks from low dose-rate (LDR) exposures to low linear-energy-transfer (low-LET) radiation. We conducted a meta-analysis of LDR epidemiologic studies that provide dose-response estimates of total solid cancer risk in adulthood in comparison to corresponding LSS risks, in order to estimate a dose rate effectiveness factor (DREF).

Materials and Methods: We identified 22 LDR studies with dose-response risk estimates for solid cancer after minimizing information overlap. For each study, a parallel risk estimate was derived from the LSS risk model using matching values for sex, mean ages at first exposure and attained age, targeted cancer types, and accounting for type of dosimetric assessment. For each LDR study a ratio of the excess relative risk per Gy (ERR Gy^{-1}) to the matching LSS ERR risk estimate (LDR/LSS) was calculated, and a meta-analysis of the risk ratios was conducted. The reciprocal of the resultant risk ratio provided an estimate of the DREF.

Results: The meta-analysis showed a LDR/LSS risk ratio of 0.36 (95% confidence interval (CI) 0.14, 0.57) for the 19 studies of solid cancer mortality and 0.33 (95% CI 0.13, 0.54) when three cohorts with only incidence data also were added, implying a DREF with values around 3, but statistically compatible with 2. However, the analyses were highly dominated by the Mayak worker study. When the Mayak study was excluded the LDR/LSS risk ratios increased: 1.12 (95% CI 0.40, 1.84) for mortality and 0.54 (95% CI 0.09, 0.99) for mortality+incidence, implying a lower DREF in the range of 1 to 2. Meta-analyses that included only cohorts in which the mean dose was <100 mGy yielded a risk ratio of 1.06 (95% CI 0.30, 1.83) for solid cancer mortality and 0.58 (95% CI 0.10, 1.06) for mortality+incidence data.

Conclusions: The interpretation of a best estimate for a value of the DREF depends on the appropriateness of including the Mayak study. This study indicates a range of uncertainty in the value of DREF between 1 and about 2

after protracted radiation exposure. The LDR data provide direct evidence regarding risk from exposures at low dose rates as an important complement to the LSS risk estimates used for radiation protection purposes.

Introduction

For many years the primary basis for risk assessment in radiation protection has been the Life Span Study (LSS) cohort of Japanese atomic bomb survivors who received a radiation exposure at a high dose rate, and in which study members with higher doses above several hundred mGy weighted absorbed colon dose have been influential in defining the LSS risk estimates. In contrast, most contemporary exposures to ionizing radiation consist of protracted exposures at low dose rates (e.g., environmental or occupational exposures) or numerous small exposures spread out over time (e.g., medical radiological examinations). It is unclear whether cancer risks estimated from an acutely exposed population accurately predict risks in populations exposed to protracted ionizing radiation.

A variety of past experimental animal studies has suggested that low-LET radiation delivered at a low rate or in many small dose fractions is less carcinogenic than the same total dose delivered as one acute exposure (Haley et al. 2015). This led to the definition of the dose rate effectiveness factor (DREF) which, along with a parallel low dose effectiveness factor (LDEF) for an acute exposure, for several decades was regarded by the International Commission on Radiological Protection (ICRP) as a combined dose and dose-rate effectiveness factor (DDREF) of 2 (reviewed in (Rühm et al. 2015a)). That is, cumulative low dose-rate (LDR) radiation exposure is regarded as causing about one half as many solid cancers as a comparable acute dose of radiation (i.e., a DDREF of 2). More recently, the National Academy of Sciences-National Research Council proposed a DDREF value of about 1.5 in BEIR VII (NAS-NRC 2006), which was criticized recently (Hoel 2015), but some now consider that the DDREF should even be about 1 and might therefore be unnecessary (SSK 2014). The historical development of our knowledge on low dose and low dose rate effects and the implications for radiological protection applications were recently reviewed in detail by Rühm et al. (2015b) including a description of the current position of various international bodies on the use of DDREF. Although a DDREF range from one to two seems small, that could be a significant factor in setting standards for radiation protection. Note that in the context of this paper a dose rate of less

than 0.1 mGy per minute, averaged over one hour, is considered a low dose rate, in line with the current definition by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR 2015). Nearly all environmental and occupational exposures are at low dose rates.

Epidemiologic studies provide the most direct evidence regarding the average DREF for radiation exposure to human populations, who are intrinsically highly heterogeneous with respect to cancer susceptibility and exposure co-factors, whereas individual experimental studies typically do not mimic that heterogeneity. However, inter-individual heterogeneity is also a weakness of epidemiologic studies, introducing random variation ("noise") into associations so that it is difficult to accurately quantify small risks from observational data. A meta-analysis can aid in this by systematically combining relevant studies so as to reduce the effects of random variation and small biases in individual studies, and thereby provide a more precise quantitative estimate of risk.

The objective of this study was to conduct a comprehensive epidemiological quantitative risk assessment of adult cancer risk from LDR exposures in comparison with the corresponding risk seen in the LSS of atomic bomb survivors. Since childhood cancers tend to be of different types than adult cancers and few studies are available of whole-body childhood radiation exposures, this analysis primarily considers adult cancer risk. This paper will consider the DREF for all solid cancer (or all cancer except leukemia), which has commonly been used as the outcome for evaluating DREF and has certain advantages. A large proportion of cancer types, including nearly all the common ones, are inducible by ionizing radiation, so this outcome includes nearly all cancer risk that an irradiated population might sustain other than leukemia and other hematopoietic malignancies. The number of solid cancers in studies is much greater than for any specific tumor site, so the statistical results have greater power and precision than those for individual tumor sites. For similar reasons, most past examinations of epidemiological data have evaluated total solid cancer risk as a radiation risk benchmark (NAS-NRC 2006; UNSCEAR 2008; Jacob et al. 2009). Radiation risk estimates for total solid cancer are also more frequently reported in epidemiologic studies than risk estimates for most individual tumor sites, so the base of potential comparisons is larger for solid cancer. Nevertheless, a similar analysis is also being performed for selected cancers and will be published separately.

The objective of the present study is to evaluate the evidence of solid cancer risks from both occupational and environmental LDR exposures. Most of the studies were based on occupational radiation exposures, which occur

mainly at low dose rates and small increments such that only a small fraction of workers accumulate whole-body doses of 100 mGy or more.

Methods

The steps to accomplish the objective of a comprehensive epidemiological quantitative assessment of solid cancer risk in LDR studies compared to the risks in the LSS were to: identify all the eligible epidemiologic LDR studies; for each LDR study calculate the ratio of its risk estimate to the risk estimate for the matching coefficient values in the LSS models, where matching was based on sex, age at first exposure or age at study entry, attained age and equivalent cancer categories, and LDR risks were compared to LSS risk estimates based on organ doses most similar to the LDR doses; perform a meta-analysis of those risk ratios, including an examination of heterogeneity of the ratios; perform sensitivity analyses to evaluate the influence of individual LDR studies upon the meta-analysis; and examine evidence pertaining to possible publication bias.

Search for eligible publications

The aim was to compile a comprehensive list of studies with dose-response analyses of LDR solid cancer data. If a study contained results only for similar cancer outcomes, but not solid cancer per se, then the outcome closest to solid cancer was chosen (hereafter referred to generically as "solid cancer"). Inclusion of leukemia was avoided because the slope and shape of the leukemia dose response differ from that for solid cancers (Hsu et al. 2013). A comprehensive search was intended in order to minimize study selection biases and publication bias. We sought to use the latest available update for each study cohort so as to maximize the information the study provides and avoid redundancy among study reports. Several approaches were used to find relevant published articles. PubMed and Google Scholar were searched, most recently in May 2016, using the search string "'ionizing radiation' AND ('epidemiology' OR 'cancer incidence' OR 'cancer mortality')". The PubMed search was fairly sensitive (detecting relevant papers) but not specific (many irrelevant papers found). In addition, references in the identified publications and in the tables of the UNSCEAR (UNSCEAR 2008) and BEIR (NAS-NRC 2006) reports plus the 15-country study (Cardis et al. 2007; Vrijheid et al. 2007) were scanned to identify additional relevant papers, augmented by personal knowledge of the literature. The goal of the search was to identify all the LDR studies since 1980 of primarily low-LET radiation that reported risk estimates for total solid cancer that were based on dose-response analyses via internal comparisons of individual dose data and provided estimates of ERR per unit dose (i.e., Sv^{-1} or Gy^{-1}).

Abstracts and articles were reviewed to determine their applicability. Because the objective was quantitative, studies lacking sufficient dose information or those with a large potential for bias were eliminated. Specifically, the following types of studies were excluded: studies lacking individual dose estimates or lacking individual data altogether (e.g., ecological studies, which may be seriously biased (Piantadosi et al. 1988)); studies based on comparisons of exposed workers with the general population (standardized mortality/incidence ratio studies, SMRs/SIRs) or of the aggregate exposed group compared with an unexposed group, because those studies potentially provide uninformative or biased estimates of risk. Also excluded were studies of childhood radiation risks. Nested case-control studies of solid cancer radiation effects, such as (Schubauer-Berigan et al. 2015), were potentially eligible since their results, when methodologically sound, are comparable to full cohort studies.

We were able to find 19 eligible cohorts with quantitative mortality risk analyses, and an additional three cohorts with only incidence risk analyses. For nine studies the endpoint analyzed was solid cancer, for ten it was all cancer except leukemia, and for one each it was, "solid cancers except liver, lung and bone" (due to Pu exposure) (Sokolnikov et al. 2015), "all cancer except leukemia or liver" (due to endemic liver cancer) (Tao et al. 2012), or "all cancer except leukemia and alcohol related cancers" (i.e., excluding liver, oropharynx and esophagus, where alcohol-related cancer risk showed a strong negative association with dose) (Akiba and Mizuno 2012). As detailed below, matching LSS risk estimates were calculated for the specific LDR study cancer endpoint.

The most common LDR studies were those of occupationally exposed cohorts; about 85% of study subjects fell into this broad category, which included cohorts of workers in nuclear weapons and processing facilities, commercial nuclear power plants, clean-up and restoration work, or a combination of these (Table 1, studies 1-17). Four other studies were based on elevated environmental exposure from high natural radiation background (Yangjiang, China (Tao et al. 2000; 2012) and Kerala, India (Nair et al. 2009; Akiba 2013)) or significant manmade sources (Techa River residents exposed to Mayak effluents (Eidemüller et al. 2010; Schonfeld et al. 2013) and Taiwan residents of radiocontaminated buildings (Hwang et al. 2006; 2008)) (Table 1, studies 18-21).

[Table 1 near here]

It was necessary to minimize the potential for data redundancy in the inclusion of study reports, for instance, a report as both an individual study and as part of a pooled analysis, or multiple reports over time of updated cohort results. When a pooled study was based on the most recent data available for the respective cohorts included, the

pooled results were used, though a secondary analysis of individual studies was also examined (e.g., the INWORKS pooled study of US, UK and French nuclear workers (Richardson et al. 2015) was included in the main analyses rather than the intra-country reports that it pooled (Muirhead et al. 2009; Metz-Flamant et al. 2013; Schubauer-Berigan et al. 2015)). However, in the case of older pooled studies such as the 15-country study (Cardis et al. 2007), several of the important cohorts of that study have since been expanded and significantly updated, so the latest reports of the studies were included rather than the dated pooled analysis. In addition, the British Nuclear Fuels Limited (BNFL) component which constitutes about 50% of the UK National Registry for Radiation Workers (NRRW), has been updated four years (Gillies and Haylock 2014) beyond the full NRRW publication (Muirhead et al. 2009), but since analyses of the NRRW data were not available separately for BNFL and non-BNFL facilities, the full NRRW analyses were preferred instead of separate BNFL analyses. Similarly, there have been several reports of overlapping but not identical cohorts for the Canadian National Dose Registry (Ashmore et al. 1998; Sont et al. 2001; Zablotska et al. 2004; 2013b); only the most recent report was included, both to avoid redundancy and to prevent dose measurement bias which was present in the earlier Canadian data.

A final source of redundancy is when both cancer incidence and mortality have been reported for a cohort. The decision was made to give preference to mortality analyses, to compare with the most recent LSS mortality data (Ozasa et al. 2012). However, an alternate analysis included the mortality results when available plus the incidence results for the three cohorts for whom only quantitative incidence data have been reported (studies 20-22 in Tables 1 and 2), in order to have the fullest representation of LDR studies with radiation risk coefficients. Justification for combining cancer mortality and incidence was provided in the BEIR VII Report (NAS-NRC 2006) which found that for nearly all cancer sites examined, the dose-response slopes were reasonably similar for mortality and incidence analyses in the LSS.

Conversion of $H_p(10)$ and other dosimetry to LSS organ doses

The solid cancer risk estimates for the LSS cohort have been reported based on weighted absorbed colon doses (Ozasa et al. 2012), while most of the LDR studies reported risk estimates based on personal dose equivalent $H_p(10)$ or other dose bases. Usually radiation dosimeters used in occupational radiation protection are calibrated in terms of $H_p(10)$, an operational dose quantity introduced by the International Commission on Radiation Units and Measurements that should provide a conservative estimate of effective dose. $H_p(10)$ is defined at a depth of 10 mm in

soft tissue beneath the dosimeter. When the risk estimate of a given LDR study was compared to that of the matched LSS risk estimates, comparison was made based on the same or the closest organ dose to that in the LDR study. For an LDR study with either $H_p(10)$, skin dose or whole-body dose, the corresponding LSS estimate was based on breast dose using an appropriate dose conversion factor; for an LDR study that reported an estimate based on effective dose, conversion was made to an estimated colon dose for comparison with the LSS; for an LDR study reporting colon or stomach doses that same organ was used for the LSS risk comparison. For dose conversions, the coefficients were based on those published in Zankl (1999) and ICRP Publication 116 (2010).

For example, for $H_p(10)$ doses, conversion coeffcients ($H_p(10)$ per air kerma in Sv/Gy) were taken from (Zankl 1999) who had calculated coefficients for various positions on the human chest. We used coefficients calculated for a typical dosimeter position, with rotational geometry. These coefficients were divided by the corresponding ICRP Publication 116 (2010) male and female conversion coefficients for the breast (absorbed breast dose per air kerma in Sv/Gy) for the same energy range and geometry. An average ratio was calculated separately for males and females, and the sex-averaged ratio of 1.01 was obtained. Then the LDR/LSS ratio corresponding to any study that reported $H_p(10)$ doses was based on an analysis using breast doses multiplied by 1.01 in the tabulated LSS data. For studies that reported effective dose estimates, the similarly-calculated conversion factor to absorbed colon dose was 0.94.

The sources of dosimetry data varied among the cohorts, ranging from film/thermoluminescent dosimeter badge data for nearly all cohort members and all study years, to dose extrapolations applied to fractions of person-time that lacked dosimeter data, to entirely retrospective estimated dose reconstructions based on limited ambient environmental measurements and modeling (e.g., (Nair et al. 2009; Tao et al. 2012)) or a job-exposure-matrix (e.g., (Kreuzer et al. 2015)) to derive individualized doses. These successive scenarios represent increasing uncertainty, but adequate information to take the dosimetric uncertainties into account in the analyses was not available. However, individualized doses were regarded as important criteria for inclusion; a study that assigned to individual study members the estimated average yearly dose of all workers at all study facilities was considered inadequate for inclusion (Sun et al. 2016). An additional study of those downwind of the Semipalatinsk nuclear bomb testing site (Bauer et al. 2005) is currently under extensive dosimetry revision (B Grosche, personal communication, 2015) so was not included.

Deriving the ratio of LDR risk to LSS risk for each study

For each included LDR study the starting point was the published point estimate of the ERR per Gy of solid cancer and its confidence interval (CI), calculated based on the assumption of a linear dose response. However, when a lower confidence bound on the ERR was indicated as not calculable in the published report, it was estimated here by assuming arithmetic symmetry of the upper and lower bounds around the point estimate. When a loglinear Cox regression model was used to estimate the hazard ratio (HR) at 100 mGy (e.g.,(Hwang et al. 2008; Boice et al. 2011)) instead of an ERR estimate per Gy, the value of HR – 1 was used to extrapolate linearly to 1 Gy, since at low doses estimates based on loglinear and linear models are usually similar (Cardis et al. 2007).

To derive a ratio of the risk in LDR cohorts to that in the atomic bomb LSS cohort, the risk estimate for each individual LDR dose-response study was compared with the risk estimate for the corresponding age and sex values of LSS models based on the corresponding organ doses (Jacob et al. 2009). Study-specific parallel endpoints were analyzed in the LSS. The models for solid cancer risk in the LSS atomic bomb cohort vary by sex, age at exposure and age attained and various categories of cancer, so the LLS risk coefficients that correspond to various LDR cohorts were tailored to the characteristics of each cohort. The latest LSS reports for mortality (Ozasa et al. 2012) and incidence (Preston et al. 2007) with available detailed tabulations were used for the matching cancer endpoints (e.g., mortality/incidence of solid cancer or all cancer except leukemia). It was not possible to derive from the LDR publications the full matrix of person-years by sex, age at exposure and attained age, so the approximations of mean ages at study entry and at the end of follow-up, and the proportion of females were used to generate an LSS risk estimate corresponding to that for each individual study.

Meta-analysis methods

The LDR/LSS ratios of the respective ERR Gy^{-1} for the LDR studies with the corresponding values derived from the LSS cohort of atomic bomb survivors were then combined to form a best estimate with a statistical meta-analysis. The basic methodologies for the comparisons and meta-analysis are described in Jacob et al (2009). Specifically, calculations of the LSS ERR per unit dose applied a conventional linear ERR model for the hazard for sex *s*, age at first exposure or study entry *e*, attained age *a* and dose *d* with a weighting factor of 10 for neutrons, where the organ dose used for the LSS analysis was as defined above for each LDR study,

$$h(e, a, s, d) = h_0(e, a, s)\,(1 + ERR(e, a, s, d)),$$

with baseline risk models, $h_0(s, e, a)$, and ERR per unit dose models, $ERR(e, a, s, d)$, as already applied in (Ozasa et al. 2012) for the mortality data and in (Preston et al. 2007) for the incidence data for the full follow-up periods:

$$ERR = (\beta d) \bullet \exp(\tau (e - e_0) + \nu \ln(a/a_0)) \bullet (1 + \sigma s),$$

where β is the coefficient for the dose range. The published model was re-optimized based on the full LSS data to match each of the LDR studies by re-centering the radiation effect modifiers for age at exposure, attained age and sex (fit parameters τ, ν and σ, respectively), using the values for the centering constants, e_0, a_0 and indicator variable s, consistent with the mean age at first exposure or study entry, mean attained age and gender proportions in each LDR study. The optimization used the corresponding cancer endpoint (e.g., solid cancer, all cancer except leukemia, etc) and LSS organ doses – e.g., breast doses when the original doses were $H_p(10)$, as described above. Model optimization was done with Poisson regression of the cross-tabulated LSS mortality or incidence data, as appropriate, using the AMFIT module of the EPICURE software package (Preston et al. 1993).

The LDR/LSS ratio q_i of the ERR per unit dose from an individual study *i* on LDR exposure, ERR_{LDRi}, to its corresponding ERR from the atomic bomb survivors, ERR_{LSSi}, was calculated as $q_i = ERR_{LDRi} / ERR_{LSSi}$, and the variance V_i of the ratio q_i was calculated by the standard method for propagation of errors (Bevington and Robinson 2003).

Methods to evaluate risk heterogeneity

The array of study ERR slope ratios (LDR_i/LSS_i) and their joint CI for the eligible studies were subjected to a meta-analysis, with and without the assumption of heterogeneity of risk ratios, along with a statistical test for heterogeneity (reviewed in (Sutton and Higgins 2008)). The pooled, inverse-variance weighted mean ratio Q of the q_i study to LSS estimates was calculated from all individual q_i studies under the basic premise that the average of estimates provided by the pooled studies is a better estimate than those provided by any of the individual studies. Cochran's Q statistic (and corresponding p value) method was applied to test for heterogeneity among study risk estimates and the DerSimonian-Laird method (1986, 2015) was applied for pooling heterogeneous groups of studies and for obtaining the overall variance on Q. Since methods for assessing risk heterogeneity are in flux (Cornell et al. 2014), heterogeneity also was evaluated using the several other methods described in (DerSimonian and Kacker 2007). However, there were no indications of heterogeneity, so the results of the several methods are not reported.

Methods for sensitivity analysis

To evaluate the degree to which individual studies influenced the meta-analysis results, risk estimates were calculated when each individual study was excluded from the analysis (leave-one-out analysis). In addition, further variations on the two most influential studies, the Mayak cohort (Sokolnikov et al. 2015) and the INWORKS cohort (Richardson et al. 2015), were examined.

Publication bias analyses

If studies with small or negative risks remain unpublished, this could result in publication bias indicated by asymmetric funnel plots (Sterne and Egger 2001; 2011). (For each study the estimate of risk is plotted against a measure of the study's precision. If there is no publication bias, the plot of the risk estimate points resembles an inverted symmetrical funnel, whereas asymmetry around the funnel axis in the study risk estimates suggests publication bias.) Publication bias was formally assessed using two analytic methods: Egger regression test (Egger et al. 1997) to detect funnel plot asymmetry by testing whether the observed outcomes are related to their corresponding sampling variances; and the trim and fill method that applies a nonparametric (rank-based) data augmentation technique to estimate how many negative studies may be missing and their potential impact on the risk estimates (Duval and Tweedie 2000).

The report methods are consistent with the PRISMA guidelines for meta-analyses (Moher et al. 2009). The authors report no conflicts of interest.

Results

Descriptive Results

Table 1 provides descriptive information on the 19 most recent, non-redundant reports of individual or pooled LDR cohorts we identified that have dose-response based risk estimates for solid cancer mortality plus three more with only incidence data (studies 20-22). The mortality studies included over 800,000 individuals, 30,000 cancer cases and a collective dose of over 33,000 person-Sv. When the three incidence studies also were included, the respective numbers were about 900,000 individuals, 32,000 cancers and 45,000 person-Sv. Of the individuals in the mortality and incidence cohorts, about 85% were from occupational cohorts for whom exposures began in adulthood, and the

vast majority were males; the others were subjected to elevated environmental exposures (studies 18-21 in Tables 1 and 2) from high natural background radiation or manmade radiation.

As shown in Table 2, 15 of the 19 solid cancer mortality studies and 2 of the 3 cancer incidence studies reported mean doses under 50 mGy, indicating they were low-dose as well as low dose-rate studies. Exposure distributions were highly skewed in the occupational studies, with small percentages of study subjects who had received up to several hundred mGy. The estimated reported mean occupational doses ranged from 6 to 134 mGy, except for the Mayak study with a mean colon dose of 354 mGy. This compares to a mean weighted absorbed colon dose of about 230 mGy in the LSS subset with >5 mGy. Of the environmental exposure studies, the reported mean doses ranged from 35 to 63 mGy, other than the Kerala study with 161 mGy. Note that in the second column of Table 2, the type of dose quantity used in the identified LDR studies is explicitly specified in a footnote.

[Table 2 near here]

Individual Study Results

The first question to address is whether there is risk after exposures at low dose rates and with low-to-moderate cumulative doses. The larger LDR studies (those with >200 solid cancer deaths) tend to provide more stable estimates of radiation risk. Of the 11 LDR studies with >200 solid cancer deaths (studies 1-9, 18-19 in Table 2), nine had positive risk coefficients, suggesting there are radiation effects after exposures at low dose rates with low-to-moderate cumulative doses. A forest plot of the ERR Gy^{-1} risk estimates for solid cancer mortality for the studies with >200 solid cancer deaths is shown in Figure 1.

[Figure 1 near here.]

The primary question with regard to the DREF is whether the LDR risk coefficients are as great (indicating a DREF of 1) or smaller (DREF >1) than corresponding risk coefficients in the LSS, where the LSS data provide the best measure of risk after a single, acute exposure ranging up to 4 Gy. A forest plot of the LDR/LSS risk ratios for solid cancer mortality in the larger studies is shown in Figure 2. The point estimates of the LDR/LSS risk ratios for four of the 11 studies with >200 deaths were ≥1, implying a DREF of about 1, while 6 of the 11 were ≤0.5 which was more compatible with a DREF of ≥2 (Table 2). However, a meta-analysis provides a weighted overall estimate of the LDR/LSS risk ratio as a more appropriate synthesis of the study results.

[Insert Figure 2 near here.]

Primary meta-analyses of risk estimates and LDR/LSS risk ratios

Using all 19 of the mortality studies shown in Table 2, the estimate of ERR Gy^{-1} was 0.15 (95% CI 0.07, 0.24) for the fixed-effects meta-analysis. The overall meta-analysis estimate of the ratio of mortality risk in the LDR studies to the corresponding risk in the LSS cohort (LDR/LSS) was 0.36 (95% CI 0.14, 0.57) (Table 3, Part A). Since the test for heterogeneity of the risk ratios was not close to statistical significance (p=0.92), a random-effects estimate was not considered. However, in this meta-analysis the Mayak worker cohort, with a low point estimate of the ERR Gy^{-1} (0.12, 95% CI 0.03, 0.21), had a very high influence: it accounted for 91% of the total weight (defined as the percentage of the total variance accounted for) in the analysis because of its narrow CI (Table 2)). No other study accounted for as much as 5% of the total weight (Table 3, Part A), so the low risk estimate in the Mayak cohort (Table 2) essentially defined the results.

[Insert Table 3 near here.]

To obtain the broadest possible assessment of LDR radiation risk, further analyses were conducted of the 22 studies that included all the mortality studies plus the three LDR studies of only solid cancer incidence ("mortality+incidence"). This meta-analysis yielded an ERR Gy^{-1} risk estimate of 0.15 (95% CI 0.06, 0.23) and a LDR/LSS risk ratio of 0.33 (95% CI 0.13, 0.54) (Table 3, Part A). The results of this analysis were similar to those for mortality studies only, but in this case the Mayak study had a lesser weight of 80%. Again there was no statistical evidence of between-study heterogeneity of the risk ratios (p=0.71).

To focus on the most common range of today's exposures in occupational, environmental or medical diagnostic settings, we further analyzed only the 16 solid cancer mortality studies with mean doses <100 mGy (which excluded the Mayak, Port Hope and Chernobyl studies); all except the Yangjiang, China study of high natural background radiation had mean doses <50 mGy (see Table 2). The meta-analytic average ERR Gy^{-1} was 0.41 (95% CI 0.12, 0.71). The meta-analytic LDR/LSS risk ratio estimate was then 1.06 (95% CI 0.30, 1.83), with no indication of risk heterogeneity (p=0.99). For the 18 mortality+incidence studies with mean doses <100 mGy, the LDR/LSS ratio was 0.58 (95% CI 0.10, 1.06). The LDR/LSS risk ratios imply a likely DREF value of between 1 and 2 at low doses, consistent with the overall results.

Sensitivity analyses of the meta-analysis results

Since the studies with the largest influence in the meta-analysis are critical in determining the assessment of DREF, sensitivity analyses by excluding each study in turn were used to judge the direction and degree of influence of the individual studies. Part A of Table 3 shows for solid cancer mortality and the mortality+incidence data the results when studies that had at least a 2% weight in the meta-analysis were individually excluded. For the mortality data the only study with a weight >10% was the Mayak study. When this study was excluded, the LDR/LSS risk ratio changed noticeably, from 0.36 (95% CI 0.14, 0.57) to 1.12 (95% CI 0.40, 1.84). Exclusion of the next most influential studies, the INWORKS and Techa River cohorts, had very little impact on the risk ratio.

Exclusion of the Mayak study from the mortality+incidence meta-analysis also produced some change in the LDR/LSS risk ratio, from 0.33 (95% CI 0.13, 0.54) to 0.54 (95% CI 0.09, 0.99) (Table 3, Part A). Exclusion of the other studies with >2% weight, namely studies of Taiwanese residents in radiocontaminated buildings, INWORKS nuclear workers and Techa River residents, had minor impacts on the risk ratio.

The leverage of the Mayak cohort was very high owing to its low point estimate and narrow CI, so its influence was examined in more depth. The narrow CI was primarily because it had a much wider dose distribution than any other LDR study (with a mean dose about 10 times as high as the average for the other mortality studies), along with a long follow-up and substantial number of solid cancer deaths. Substantial ^{239}Pu exposures were sustained by some of the workers in the early days, but only about 40% of workers with probable exposure had personal ^{239}Pu measurements (Sokolnikov et al. 2015). Even though the primary target organs of ^{239}Pu, the lung, liver and bone, were excluded from the analysis (Sokolnikov et al. 2015), both the uncertain ^{239}Pu exposures and the likelihood that the external dosimetry was less accurate in the 1940s and early 1950s (Vasilenko et al. 2007b) could have influenced the risk estimates of other organs. In response to the concern about uncertain ^{239}Pu exposure data, a re-analysis was conducted that excluded workers from the plutonium and radiochemical plants, the two plants at Mayak that provided substantial ^{239}Pu exposures, in order to assess risk among the subcohort of workers with essentially no ^{239}Pu exposure (Sokolnikov et al. 2016). About 70% of the total workers worked at those two plants. The resulting estimate of ERR Gy^{-1} was 0.20 (95% CI -0.0002, 0.46) for solid cancer mortality. The Mayak non-Pu cohort accounted for 63% of the total weight in that analysis and two others had weights >10% (Part B of Table 3). With the two Pu facilities excluded, the mortality meta-analysis of the LDR/LSS ratios of risk yielded 0.71 (95% CI

0.27, 1.15), again with no indication of significant inter-study variability (p=0.98). When the combined mortality and incidence studies were analyzed, excluding the two Mayak Pu plants, the estimated ERR Gy^{-1} was 0.26 (95% CI 0.10, 0.42) and the ratio of the LDR/LSS risks was 0.54 (95% CI 0.09, 0.99).

Since the INWORKS study represented a combination of already-pooled studies in the US, UK and France and had some variation in risk coefficients depending on which covariates were included in the analyses, the influence of this study was also examined in more detail by conducting meta-analyses that included the separate US, UK and France results rather than INWORKS. Because INWORKS had relatively more weight when the Mayak plutonium subcohort was excluded, rather than the full Mayak cohort, we examined that scenario for the comparison of the LDR/LSS risk ratios using the INWORKS study (Richardson et al. 2015) to those using the separate UK, US and France pooled analysis studies (Muirhead et al. 2009; Metz-Flamant et al. 2013; Schubauer-Berigan et al. 2015). For solid cancer mortality the meta-analytic LDR/LSS ratio was 0.71 (95% CI 0.27, 1.15) using the INWORKS study and 0.64 (95% CI 0.23, 1.06) using the three separate studies. For mortality+incidence the values of the LDR/LSS ratio were 0.51 (95% CI 0.16, 0.86) and 0.48 (95% CI 0.14, 0.82), respectively. For analyses for which the full Mayak cohort was included, there was essentially no difference between including the INWORKS or the separate UK, US and France studies (data not shown). We concluded that using the INWORKS results compared to those from the separate countries made little difference in the meta-analysis results.

Publication bias

The funnel plots showed almost no asymmetry (not shown) and the Egger regression analysis did not approach significance, indicating little or no publication bias (Egger et al. 1997). The trim and fill method (Duval and Tweedie 2000) indicated that one or two small negative studies might theoretically be missing in the various meta-analyses considered, but the impact of those theoretical studies on the meta-analysis results was immaterial. Therefore, there was no indication that the estimates for the pooled risk ratios presented here were more than marginally affected by publication bias.

Discussion

This study attempted to assemble and analyze all the quantitative data regarding radiation risk for human total solid cancer in adults following protracted radiation exposures. A number of other studies of irradiated populations have been published but are unsuitable for quantitative analysis because of either missing individual radiation dose information (e.g., (Berrington et al. 2001; Liu et al. 2014)) or probable biases due to "healthy worker effects" in comparing radiation workers to the general population (e.g., (Wiggs et al. 1994; Zielinski et al. 2009)). The primary goal in the present study was to compare risks quantitatively for groups with LDR exposures to the corresponding risks among the LSS of atomic bomb survivors, in order to estimate the DREF (the reciprocal of the LDR/LSS risk ratio is an estimate of DREF). Taken at face value, the results using either the mortality cohort data or both mortality and incidence cohort data are more compatible with a DREF of 1.5 or 2 than of 1, since for most meta-analyses the estimated ratios of LDR to LSS risk were <1, and for the primary analyses of solid cancer mortality or mortality+incidence the upper 95% confidence bounds were less than one (Table 3, part A), indicating there was a low probability that the estimate included one.

However, caution should be exercised in drawing the inference that the data are incompatible with a DREF of 1 because the risk ratios were so highly dominated by the Mayak worker study which had a low risk coefficient (Sokolnikov et al. 2015). It was apparent that the risk estimate for the entire Mayak cohort substantially depressed the overall LDR/LSS risk ratio (i.e., removing it notably increased the resultant risk ratio). Specifically, The LDR/LSS ratio estimate of the Mayak study was 0.28 (95% CI 0.09, 0.47). The LDR/LSS ratio estimates for the rest of the studies, excluding Mayak, were 1.12 (95% 0.40, 1.84) for mortality studies and 0.54 (95% CI 0.09, 0.99) for mortality+incidence studies. Thus the risk ratio for the Mayak study was about 2-4 times less than that for other LDR studies. The Mayak cancer incidence study by Hunter et al. (2013) reported an even lower risk estimate (ERR Gy^{-1} of 0.07 (95% CI 0.01, 0.15) and, if used, would likely have depressed the LDR/LSS risk ratio still further. (It differed from the mortality study in having four fewer years of follow-up, not having any tumor information after out-migration from Ozyorsk, not including auxiliary plant workers, using $H_p(10)$ doses rather than colon doses in analyses, and having a different mix of tumor types (due to variations in the lethality proportions of various cancers). It was not included in the analysis because of the decision to include mortality rather than incidence studies when both were available.) However, the Mayak subset without ^{239}Pu exposure had a lesser effect on the meta-analysis risk

ratios, due to the higher point estimate of the ERR Gy^{-1} and the wider 95% CI (Sokolnikov et al. 2016). The question becomes how to evaluate the weight to be accorded to the Mayak study in interpreting the results. On the one hand, the Mayak study had primarily a low dose rate and provided a more precise risk estimate (i.e., narrower CI) than other LDR studies, largely because of its wide distribution of cumulative doses. Its mean cumulative dose was about 10 times as large as the average of mean doses of the other LDR studies and was two times larger than the mean dose of the LSS. On the other hand, concerns about the Mayak study include the possible impact of unmeasured ^{239}Pu exposures, the fact that three organs (liver, lung and bone) were excluded from its solid cancer risk estimates, potential dose uncertainties among the earliest Mayak workers (Vasilenko et al. 2007b) who had the highest exposure, and the possibility that the high rate of loss to follow-up (23%) might be dose dependent. If the Mayak study is excluded, the risk ratio from the meta-analysis of LDR studies to the LSS is approximately 1, implying an estimated DREF of 1.

The other major LDR mortality study was the large INWORKS study consisting of a long-term follow-up of 308,000 workers at nuclear facilities. Papers describing the cohort and dosimetry, and evaluating leukemia and solid cancer risk, have been published to date (Leuraud et al. 2015; Richardson et al. 2015; Thierry-Chef et al. 2015; Hamra et al. 2016). As part of the study development, the dosimetry of the various cohorts was improved and harmonized (Thierry-Chef et al. 2015). We examined the impact of the INWORKS study solid cancer risk-ratio estimates because the reported risk estimates of this important study varied according to which covariates were included in the analysis (Richardson et al. 2015), and there were possibilities of missed dose. A question was whether the estimated solid cancer risk ratio of the INWORKS study was similar to that of other low-dose (<100 mGy) studies. With the INWORKS study included, the LDR/LSS average risk ratio was 1.06 (95% CI 0.30, 1.83) for the <100 mGy studies, but absent that study the estimate was 0.82 (95% CI -0.23, 1.88). Thus the INWORKS study had a higher risk estimate (see Table 2) than the average of other low dose-rate studies and had an effect on the meta-analytic risk estimate for the <100 mGy studies because of its large size. However, it cannot be determined whether the higher INWORKS risk coefficient represents a real difference, was simply a random variation in risk estimates, was attributable to uncertainties in the dosimetric estimates in the earliest years, or might reflect not having neutron and internal-emitter exposures to include in the dose estimates, which, if included and positively correlated with external dose (as one might expect), would likely reduce the risk coefficient.

This meta-analysis largely adopted the methodology that Jacob et al (Jacob et al. 2009) had developed to compare radiation worker study risks to the corresponding LSS risk estimates, so a comparison of the results of the two studies is of interest. In the main analysis of seven radiation worker mortality studies by Jacob et al, the combined worker study to LSS risk ratio was 1.21 (90% CI 0.51, 1.90), which is most compatible with a DREF of 1, but is also statistically compatible with a DREF of 1.5, but barely with a DREF of 2. Their estimated LDR/LSS risk ratio is considerably higher than our primary risk ratio of 0.36 (95% CI 0.14, 0.57). But if the Mayak study is excluded from the present meta-analysis, the resulting risk ratio (1.12, 90% CI 0.51, 1.72) is similar to that obtained by Jacob et al, who likewise did not include the Mayak study. However, it is notable that, absent the Mayak study, our 90% CI (0.51, 1.72) is narrower than the 90% CI (0.51, 1.90) of Jacob et al. Our narrower CI can be attributed to the fact that this report is based on more studies, some with longer follow-up and more solid cancers than was theirs, so it provides a more precise risk estimate. When we analyzed the mortality and incidence studies together, but excluded the Mayak study, the LDR/LSS risk ratio was 0.54 (90% CI 0.09, 0.99), suggesting a DREF of about 2.

For the four environmental exposure studies (studies 18-21 in Table 2), either a fraction of the cohort (Techa and Taiwan) or the entire cohort (Kerala and Yangjiang) had radiation exposure in childhood. In only the Techa River study was there significant evidence of excess risk for cancer. Since radiation sensitivity is thought to be greater in childhood, the null results may be associated with the low statistical power of the studies, though there are other possibilities: that very low dose-rate radiation exposures in the high natural background radiation area (HBRA) studies confer little risk; that multi-generational radiation adaptation has occurred; that in the HBRA studies the individual dose uncertainties were probably large owing to dose reconstruction limitations, which would attenuate risk estimates; that there might be confounding by sociodemographic, lifestyle or medical risk factors; or that dose-associated geographic variations in completeness of cancer ascertainment might tend to mask radiation effects.

A criticism sometimes voiced about results from low-dose studies is that most such studies have skewed dose distributions, and the higher doses in the study "drive" (i.e., disproportionately influence) the risk estimate, so that it's not fully a low-dose study. The largest study, the INWORKS cohort, examined this issue by calculating the dose-response risk for all cancers except leukemia over restricted cumulative dose ranges (Richardson et al. 2015). The ERR Gy^{-1} was 1.04 (90% CI 0.55, 1.56) for the 0-200 mGy range, 0.69 (90% CI 0.10, 1.30) for the 0-150 mGy range, and 0.81 (90% CI 0.01, 1.64) for the 0-100 mGy range. These risk estimates are all nominally higher than the

study's overall ERR Gy^{-1} of 0.48, thereby indicating that a positive risk was not contingent upon the higher doses. The results are supportive of a risk, albeit small, at relatively low doses. Like the INWORKS study, the present meta-analyses do not show any negative lower confidence bounds, even when restricted to low-dose studies, suggesting the results are not statistically compatible with hormesis or a high dose-effect threshold.

Study Strengths

We aimed for a comprehensive compilation of LDR studies that have quantitative risk estimates for adult solid cancer based on individualized doses. Beyond that requirement, the studies of over 900,000 individuals were unselected and are believed to be representative. The meta-analysis provides a "weight of evidence" regarding the quantitative risk of solid cancer from LDR irradiation with better precision than for individual studies. A bias that may be present in one study is not likely to be present in most other studies, so biases probably are attenuated or may cancel out. The methodology used here fit the LDR risk experience to the corresponding LSS risk modeling, using matching values for sex, age at exposure, attained age, targeted cancer types, and accounting for type of dosimetric assessment. Most of the larger LDR cohorts had a long period of follow-up, where lengthy observation increases the precision and applicability of risk estimates. The cancer mortality (or incidence) ascertainment was of high quality for nearly all the studies, an important element of study validity. Though there were dose uncertainties, overall the dosimetry was reasonably good since a large fraction of the person-time of most studies was based on individual badge dosimetric measurements.

Study Limitations

A few studies, particularly those conducted in areas where cancer diagnostic facilities and registration systems have been developing (Jayalekshmi et al. 2005), may have had limitations in cancer diagnosis and ascertainment, but most studies have been conducted with longstanding, good quality cancer ascertainment. The meta-analysis was conducted to increase the statistical power and precision of the risk estimates, but even with 900,000 individuals under study there are still limitations on power and precision because of the low doses of most of the LDR studies. Published risk estimates were used because individual data from the respective studies were unavailable; the published data represent variations in data compilation and analysis procedures which may have created more heterogeneity in the risk estimates. While the formal tests for heterogeneity of risk estimates were not statistically significant (Cochran's

Q test, all probabilities $p>0.7$), such tests have relatively poor statistical power, and there was an apparent discrepancy in risk estimates between the two most influential studies of the Mayak and INWORKS workers.

It was not possible to obtain the full distributions of the durations and ages of the chronic exposures and the ages at last follow-up, so the method could adjust only approximately for age factors in risk in individual studies. Similarly, the distributions of age and dose by sex were mostly unavailable, so assumptions had to be made that the distributions were similar for both sexes; dissimilarities could induce biases since the LSS male and female risk coefficients differ (Ozasa et al. 2012). A number of studies did not incorporate adjustments for employment status (employed/not-employed for given person-years) or duration of employment (where short-term workers tend to have different health experience than those with longer employment; also healthy workers tend to work longer and thereby have more opportunity for radiation exposure, which may attenuate the dose-response association). Some variations in dose-related risk estimates within studies, e.g., for BNFL (Gillies and Haylock 2014) workers with and without internal exposures, who are part of the INWORKS study (Muirhead et al. 2009; Richardson et al. 2015), suggest there could be selection effects or other unwanted sources of variation that are averaged over in the present analyses. One solid cancer incidence study with a small number of cancer cases and a fairly low dose had a very narrow CI on its risk estimate for reasons that are unclear, so that it had an unexpectedly high weight in the analyses (Hwang et al. 2008).

There were important disease risk factors that could not be adjusted for because information was unavailable in most studies—factors such as occupational/socioeconomic status, smoking and alcohol consumption histories and medical radiation exposures. Confounding/bias from unmeasured disease risk factors potentially has a greater impact in low-dose studies because the magnitude of bias (either to exaggerate or mask the true degree of association) may approach or exceed the size of the dose effect. However, it is important to note that disease risk factors would be confounders only if their frequency varied according to radiation dose. Several LDR studies have not found dose-dependent associations with smoking (Muirhead et al. 2009; Tao et al. 2012; Zablotska et al. 2013b; Sokolnikov et al. 2015), although the study of Japanese nuclear workers found indications that alcohol intake was probably inversely associated with radiation dose, and they therefore conducted analyses that excluded the primary alcohol-related cancer sites (Akiba and Mizuno 2012).

Direct comparisons of total solid cancer risk between the Japanese and western populations also have limitations. The mix of excess radiation-related cancers differs between populations; for instance, stomach cancer contributes a larger proportion of the excess cases in the Japanese LSS than it does in western studies. The transport of breast cancer risk from the LSS to western studies seems to fit an excess absolute risk (EAR) model better than an ERR model (NAS-NRC 2006). Such variations may affect the magnitude of the LDR/LSS ratios of studies in this analysis to some degree.

The study is a work in progress because more mortality and incidence data will undoubtedly be accrued, and further improvements in study dosimetry can be made. To better characterize DREF, it should also be evaluated for leukemia, individual solid cancers or cancer groupings, and for childhood exposures, as well as for adult solid cancer.

Dosimetry Uncertainties

Although the personal badge dosimetry data for some decades have been of reasonably high quality, larger dose uncertainties occurred in the pre-1960s worker data when there was probably some systematic underestimation of doses due to high limits of detection for photon radiation in combination with frequent changes of dosimeters (resulting in many readings below limits of detection), and missing film badge data. The impact of dose underestimation may have been to positively bias risk estimates, the degree of which is unknown. However, there also are concerns that early, unfiltered dosimeters, such as the ones used at Mayak until about 1954, overestimated exposures to photons because of variability in energy and angular response characteristics (Vasilenko et al. 2007a). A Mayak dose reconstruction effort attempted to make corrections for that variability (Vasilenko et al. 2007b), but the accuracy of the reconstructed doses cannot be verified. Random dosimetry measurement error usually attenuates the dose response (Gilbert 2009), though probably only to a small degree in worker cohorts, given the large number of reasonably accurate photon dosimeter measurements and the dose reconstructions to improve upon missing or poorer early measurements. Though the worker cohorts primarily received low-LET radiations and risk estimates were based on external doses (plus some tritium doses in a few studies), a subset of workers in several studies also received exposures to neutrons or internally deposited alpha-emitters, which were unaccounted for in most studies. Regarding studies with more common internal exposures: among Mayak workers the primary sites of ^{239}Pu exposure effects (lung, liver, bone) were excluded, analyses of external exposure were adjusted for concomitant ^{239}Pu exposure (Sokolnikov et al. 2015) and analyses of workers only at facilities with no ^{239}Pu exposures also were reported

(Sokolnikov et al. 2016); analyses of solid cancer by gamma exposure among German uranium millers were adjusted for radon exposures (Kreuzer et al. 2015); analyses by external exposure in the Port Hope uranium processing cohort were not adjusted for exposure to radon-decay-products (Zablotska et al. 2013a); and joint analyses of several cohorts that included Rocky Flats examined risks with and without exclusion of those with internal exposures and found no difference in risk estimates, suggesting that the internal exposures had little impact on the external radiation results (Cardis et al. 1995).

The environmental exposure studies had substantial dosimetry uncertainties because personal dose measurements typically were not available and complex dose reconstructions had to be performed, with their larger inherent uncertainties. The ambient exposure measurement errors in the environmental studies are more likely to be grouped (Berksonian) errors from imputed subgroup doses, which would tend to produce uncertainty but little bias (Stram et al. 2015), unless the imputed doses themselves were biased. However, in summary, the aggregate effect of occupational and environmental dosimetry uncertainties upon the risk estimates is not well known in either direction or degree.

Publication Bias

Publication bias can occur when journals reject null studies, when the investigator decides not to publish a null study, or when dose-response modeling is performed only if there appears to be a positive association. In this study most of the funnel plots to detect publication bias appeared symmetric, suggesting negligible bias, and the tests for asymmetry (Egger et al. 1997) were not significant. The publication bias test to detect theoretical missing negative studies (Duval and Tweedie 2000) suggested the possibility of one or two missing studies but that those studies would have little or no effect on the risk estimates. It should be noted, however, that publication bias tests have limited sensitivity and validity (Jin et al. 2015), so the null results are suggestive but not necessarily conclusive.

Conclusions

Protracted exposure to low-LET radiation at low dose rates is significantly associated with solid cancer mortality and is not suggestive of hormesis or a high dose threshold because most of the risks per unit dose in individual studies considered here were positive for this type of exposure, and the statistical lower bounds of all the meta-analyses were greater than zero. Estimates of solid cancer risk in LDR studies were compared to those observed among exposed adults in the LSS of atomic bomb survivors to evaluate DREF. The ratio of LDR to LSS solid cancer risk for all the

mortality studies was significantly less than 1 and suggestive of a DREF of approximately 2. However, without the large influence of the Mayak worker study, the ratio of LDR to LSS mortality risk was most compatible with a DREF of about 1. When eligible solid cancer incidence studies also were included, the LDR/LSS risk ratio was most compatible with a DREF of 2 regardless of whether the Mayak study was included. When only studies with mean doses under 100 mGy were analyzed, the solid cancer mortality data were suggestive of a DREF of 1, but the mortality+incidence data suggested a DREF of about 2. The quantitative assessment of solid cancer risk following protracted irradiation is broadly informative and complements the risk estimates obtained from the LSS. Nevertheless, this comprehensive meta-analysis of quantitative epidemiologic LDR data does not per se allow for an unambiguous determination of DREF because of inter-study variation in risk estimates. Determination of a numerical value of DREF ultimately requires an integration of epidemiologic data with experimental and mechanistic information to make an appropriate judgment for radiation protection purposes.

Acknowledgements

The authors would like to thank Dr. Mark Little (U.S. National Cancer Institute) for useful suggestions regarding this paper.

REFERENCES

Akiba S, Mizuno S. 2012. The third analysis of cancer mortality among Japanese nuclear workers, 1991-2001: estimation of excess relative risk per radiation dose. J Radiol Prot. 32:73-83. doi:10.1088/0952-4746/32/1/73

Akiba S. 2013. Cancer risk associated with low-dose and low-dose-rate ionizing radiation exposure. Genes Environ. 35(3):80-87. doi:30.3123/jemsge.2013.004

Ashmore JP, Krewski D, Zielinski JM, Jiang H, Semenciw B. 1998. First analysis of mortality and occupational radiation exposure based on the national dose registry of Canada. Am J Epidemiol. 148:564-574

Bauer S, Gusev BI, Pivina LM, Apsalikov KN, Grosche B. 2005. Radiation exposure due to local fallout from Soviet atmospheric nuclear weapons testing in Kazakhstan: solid cancer mortality in the Semipalatinsk historical cohort, 1960-1999. Radiat Res. 164:409-419

Berrington A, Darby SC, Weiss HA, Doll R. 2001. 100 years of observation on British radiologists: mortality from cancer and other causes 1897-1997. Br J Radiol. 74:507-519

Bevington PR, Robinson DK. 2003. Data reduction and error analysis for the physical sciences, vol Third Edition. McGraw-Hill, New York

Boice JD, Jr, Cohen SS, Mumma MT, Ellis ED, Eckerman KF, Leggett RW, Boecker BB, Brill AB, Henderson BE. 2011. Updated mortality analysis of radiation workers at Rocketdyne (Atomics International), 1948-2008. Radiat Res. 176:244-258

Cardis E, Gilbert E, Carpenter L, Howe G, Kato I, Armstrong B, Beral V, Cowper G, Douglas A, Fix J et al. 1995. Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. Radiat Res. 142:117-132

Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, Howe G, Kaldor J, Muirhead CR, Schubauer-Berigan M et al. 2007. The 15-country collaborative study of cancer risk among radiation workers in the nuclear industry: estimates of radiation-related cancer risks. Radiat Res. 167:396-416

Cornell JE, Mulrow CD, Localio R, Stack CB, Meibohm AR, Guallar E, Goodman SN. 2014. Random-effects meta-analysis of inconsistent effects: A time for change. Ann Intern Med. 160:267-270

DerSimonian R, Laird N. 1986. Meta-analysis in clinical trials. Control Clin Trials. 7:177-188

DerSimonian R, Kacker R. 2007. Random effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials. 28:105-114. doi:10.1016/j.cct.2006.04.004

DerSimonian R, Laird N. 2015. Meta-analysis in clinical trials revisited. Contemp Clin Trials. 45:139-145. doi:10.1016/j.cct.2015.09.002

Duval S, Tweedie R. 2000. A nonparametric "trim and fill" method of accounting for publication bias in meta-analysis. J Am Stat Assoc. 98:89-98

Egger M, Davey SG, Schneider M, Minder C. 1997. Bias in meta-analysis detected by a simple graphical test. Br Med J. 315:629-634

Eidemüller M, Ostroumova E, Krestinina L, Epiphanova S, Akleyev A, Jacob P. 2010. Comparison of mortality and incidence solid cancer risk after radiation exposure in the Techa River Cohort. Radiat Environ Biophys. 49:477-490

Gilbert ES. 2009. The impact of dosimetry uncertainties on dose-response analyses. Health Phys. 97:487-492

Gillies M, Haylock R. 2014. The cancer mortality and incidence experience of workers at British Nuclear Fuels plc, 1946-2005. J Radiol Prot. 34:595-623

Haley BM, Paunesku T, Grdina DJ, Woloschak GE. 2015. The increase in animal mortality risk following exposure to sparsely ionizing radiation is not linear quadratic with dose. PLoS One. 10(12):e0140989. doi:10.1371/journal.pone.0140989

Hamra GB, Richardson DB, Cardis E, Daniels RD, Gillies M, O'Hagan J, Haylock R, Laurier D, Leuraud K, Moissonnier M et al. 2016. Cohort profile: the International Nuclear Workers Study (INWORKS). Int J Epidemiol. 45(3):693-699. doi:10.1093/ije/dyv122

Hoel DG. 2015. Comments on the DDREF estimate of the BEIR VII Committee. Health Phys. 108(3):351-356. doi:10.1097/HP.0000000000000189

Hsu W-L, Preston D, Soda M, Sugiyama H, Funamoto S, Kodama K, Kimura A, Kamada N, Dohy H, Tomonaga M et al. 2013. The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950-2001. Radiat Res. 179:361-382

Hunter N, Kuznetsova IS, Labutina EV, Harrison JD. 2013. Solid cancer incidence other than lung, liver and bone in Mayak workers: 1948-2004. Br J Cancer. 109:1989-1996

Hwang S-L, Guo H-R, Hsieh W-A, Hwang J-S, Lee S-D, Tang J-L, Chen C-C, Chang T-C, Wang J-D, Chang WP. 2006. Cancer risks in a population with prolonged low dose-rate gamma-radiation exposure in radiocontaminated buildings, 1983-2002. Int J Radiat Biol. 82(12):849-858. doi:10.1080/09553000601085980

Hwang S-L, Hwang J-S, Yang Y-T, Hsieh WA, Chang T-C, Guo H-R, Tsai M-H, Tang J-L, Lin I-F, Chang WP. 2008. Estimates of relative risks for cancers in a population after prolonged low-dose-rate radiation exposure: a follow-up assessment from 1983 to 2005. Radiat Res. 170:143-148

ICRP. 2010. Conversion coefficients for radiological protection quantities for external radiation exposures. Internation Commission on Radiological Protection, Publication 116. Ann ICRP. 40(2-5)

Jacob P, Rühm W, Walsh L, Blettner M, Hammer G, Zeeb H. 2009. Cancer risk of radiation workers larger than expected? Occup Environ Med. 66:789-796

Jayalekshmi P, Gangadharan P, Vinu VS, Nair RRK, Nair MK, Rajan B, Akiba S. 2005. What did we learn from epidemiological studies in high background radiation areas in India. Int Congress Series. 1276:102-105. doi:10.1016/j.ics.2004.11.192

Jin Z-C, Zhou X-H, He J. 2015. Statistical methods for dealing with publication bias in meta-analysis. Statist Med. 34:343-360. doi:10.1002/sim.6342

Kreuzer M, Dufey F, Laurier D, Nowak D, Marsh JW, Schnelzer M, Sogl M, Walsh L. 2015. Mortality from internal and external radiation exposure in a cohort of male German uranium millers, 1946-2008. Int Arch Occup Environ Health. 88(4):431-441. doi:10.1007/s00420-014-0973-2

Leuraud K, Richardson DB, Cardis E, Daniels RD, Gillies M, O'Hagan JA, Hamra GB, Haylock R, Laurier D, Moissonnier M et al. 2015. Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study. Lancet Haematol. 2(7):e276-e281. doi:10.1016/S2352-3026(15)00094-0

Liu JJ, Freedman DM, Little MP, Doody MM, Alexander BH, Kitahara CM, Lee T, Rajaraman P, Miller JS, Kampa DM et al. 2014. Work history and mortality risks in 90 268 US radiological technologists. Occup Environ Med. 71(12):819-835. doi:doi:10.1136/oemed-2013-101859

Metz-Flamant C, Laurent O, Samson E, Caer-Lorho S, Acker A, Hubert D, Richardson DB, Laurier D. 2013. Mortality associated with chronic external radiation exposure in the French combined cohort of nuclear workers. Occup Environ Med. 70:630-638. doi:10.1136/oemed-2012-101149

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 62:1006-1012. doi:10.1016/j.jclinepi.2009.06.005

Muirhead CR, O'Hagan JA, Haylock RGE, Phillipson MA, Willcock T, Berridge GLC, Zhang W. 2009. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. Br J Cancer. 100:206-212

Nair RRK, Rajan B, Akiba S, Jayalekshmi P, Nair MK, Gangadharan P, Koga T, Morishima H, Nakamura S, Sugahara T. 2009. Background radiation and cancer incidence in Kerala, India - Karunagappally cohort study. Health Phys. 96:55-66

NAS-NRC. 2006. Health Risks From Exposure to Low Levels of Ionizing Radiation: BEIR VII. Phase 2. National Academies Press, Washington, DC

Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, Sakata R, Sugiyama H, Kodama K. 2012. Studies of the mortality of atomic bomb survivors, Report 14, 1950-2003: an overview of cancer and noncancer diseases. Radiat Res. 177:229-243

Piantadosi S, Byar D, Green S. 1988. The ecological fallacy. Am J Epidemiol. 127:893-904

Preston DL, Lubin JH, Pierce DA (1993) Epicure Users Guide. HiroSoft International Corporation, Seattle, WA

Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K. 2007. Solid cancer incidence in atomic bomb survivors: 1958-1998. Radiat Res. 168:1-64

Richardson DB, Cardis E, Daniels RD, Gillies M, O'Hagan JA, Hamra GB, Haylock R, Laurier D, Leuraud K, Moissonnier M et al. 2015. Risk of cancer from occcupational exposure to ionising radiation: retrospective cohort study of workers in France, the United Kingdom, and the United States (INWORKS). Br Med J. 351:h5359. doi:10.1136/bmj.h5359

Rühm W, Azizova TV, Bouffler SD, Little MP, Shore RE, Walsh L, Woloschak GE. 2015a. Dose rate effects in radiation biology and radiation protection. Ann ICRP. 45:262-279. doi:10.1177/0146645316629336, PMID 26343037

Rühm W, Woloschak GE, Shore RE, Azizova TV, Grosche B, Niwa O, Akiba S, Ono T, Suzuki K, Iwasaki T et al. 2015b. Dose and dose rate effects of ionizing radiation: a discussion in the light of radiological protection. Radiat Environ Biophys. 54:379-401. doi:10.1007/s00411-015-0613-6

Schonfeld SJ, Krestinina LY, Epifanova S, Degteva MO, Akleyev AV, Preston DL. 2013. Solid cancer mortality in the Techa River cohort (1950-2007). Radiat Res. 179:183-189

Schubauer-Berigan MK, Daniels RD, Bertke SJ, Tseng CY, Richardson DB. 2015. Cancer mortality through 2005 among a pooled cohort of U.S. nuclear workers exposed to external ionizing radiation. Radiat Res. 183(6):620-631. doi:10.1667/RR13988.1

Sokolnikov M, Preston D, Stram D. 2016. Mortality from solid cancers other than lung, liver and bone in relation to external dose among plutonium and non-plutonium workers in the Mayak Worker Cohort. Radiat Environ Biophys. Available online. doi:10.1007/s00411-016-0670-5

Sokolnikov ME, Preston D, Gilbert E, Schonfeld S, Koshurnikova NA. 2015. Radiation effects on mortality from solid cancers other than lung, liver, and bone cancer in the Mayak worker cohort: 1948-2008. PLoS One. 10(2):e0117784. doi:10.1371/journal.pone.0117784

Sont WN, Zielinski JM, Ashmore JP, Jiang H, Krewski D, Fair ME, Band PR, Letourneau EG. 2001. First analysis of cancer incidence and occupational radiation exposure based on the national dose registry of Canada. Am J Epidemiol. 153:309-318

SSK (2014) Dose- and Dose-rate-effectiveness factor (DDREF), Recommendation by the German Commission on Radiological Protection with Scientific Grounds

Sterne JAC, Egger M. 2001. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol. 54:1046-1055

Sterne JAC, Sutton AJ, Ioannidas JPA, Terrin N, Jones DR, Lau J, Carpenter J, Rücker G, Harbord RM, Schmid CH et al. 2011. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. Br Med J. 342:d4002. doi:10.1136/bmj.d4002

Stram DO, Preston DL, Sokolnikov M, Napier B, Kopecky KJ, Boice JD, Beck H, Till J, Bouville A. 2015. Shared dosimetry error in epidemiological dose-response analyses. PLoS One. 10(3):e0119418. doi:10.1371/journal.pone.0119418

Sun Z, Inskip PD, Wang J, Kwon D, Zhao Y, Zhang L, Qin W, Fan S. 2016. Solid cancer incidence among Chinese medical diagnostic x-ray workers, 1950-1995: estimation of radiation-related risks. Int J Cancer. 138(12):2875-2883. doi:10.1002/ijc.30036

Sutton AJ, Higgins JPT. 2008. Recent developments in meta-analysis. Statist Med. 27:625-650. doi:10.1002/sim.2934

Tao Z, Zha Y, Akiba S, Sun Q, Zou J, Li J, Liu Y, Kato H, Sugahara T, Wei L. 2000. Cancer mortality in the high background radiation areas of Yangjiang, China during the period between 1979 and 1995. J Radiat Res. 41 (Suppl):31-41

Tao Z, Akiba S, Zha Y, Sun Q, Zou J, Li J, Liu Y, Yuan Y, Tokonami S, Morishima H et al. 2012. Cancer and non-cancer mortality among inhabitants in the high background radiation area of Yangjiang, China (1979-1998). Health Phys. 102(2):173-181

Thierry-Chef I, Richardson DB, Daniels RD, Gillies M, Hamra GB, Haylock R, Kesminiene A, Laurier D, Leuraud K, Moissonnier M et al. 2015. Dose estimation for a study of nuclear workers in France, the United Kingdom and the United States of America: methods for the International Nuclear Workers Study. Radiat Res. 183(6):632-642

UNSCEAR. 2008. Sources and Effects of Atomic Radiation. Annex A: Epidemiological studies of radiation and cancer. In: Effects of Ionizing Radiation - UNSCEAR 2006 Report, vol 1. New York, pp 13-322

UNSCEAR. 2015. UNSCEAR 2012 Report to the General Assembly, with Scientific Annexes. United Nations, New York

Vasilenko EK, Khokhryakov VF, Miller SC, Fix JJ, Eckerman K, Choe DO, Gorelov M, Khokhryakov VV, Knyasev V, Krahenbuhl MP et al. 2007a. Mayak worker dosimetry study: an overview. Health Phys. 93:190-206

Vasilenko EK, Knyazev V, Gorelov M, Smetanin M, Scherpelz RI, Fix JJ. 2007b. Mayak film dosimeter response studies, part 1: measurements. Health Phys. 93(3):220-230

Vrijheid M, Cardis E, Blettner M, Gilbert E, Hakama M, Hill C, Howe G, Kaldor J, Muirhead CR, Schubauer-Berigan M et al. 2007. The 15-country Collaborative Study of cancer risk among radiation workers in the nuclear industry: design, epidemiological methods and descriptive results. Radiat Res. 167:361-379

Wiggs LD, Johnson E, Cox-DeVore C, Voelz G. 1994. Mortality through 1990 among white male workers at the Los Alamos National Laboratory: considering exposures to plutonium and external ionizing radiation. Health Phys. 67:577-588

Zablotska LB, Ashmore JP, Howe GR. 2004. Analysis of mortality among Canadian nuclear power industry workers after chronic low-dose exposure to ionizing radiation. Radiat Res. 161:633-641

Zablotska LB, Lane RS, Frost SE. 2013a. Mortality (1950-1999) and cancer incidence (1969-1999) of workers in the Port Hope cohort study exposed to a unique combination of radium, uranium and gamma-ray doses. BMJ Open. 3(2):e002159. doi:10.1136/bmjopen-2012-002159

Zablotska LB, Lane RSD, Thompson PA. 2013b. A reanalysis of cancer mortality in Canadian nuclear workers (1956-1994) based on revised exposure and cohort data. Br J Cancer. 110:214-223. doi:10.1038/bjc.2013.592

Zankl M. 1999. Personal dose equivalent for photons and its variation with dosimeter position. Health Phys. 76(2):162-170

Zielinski JM, Garner MJ, Band PR, Krewshi D, Shilnikova NS, Jiang H, Ashmore JP, Sont WN, Fair ME, Letourneau EG, Semenciw R. 2009. Health outcomes of low-dose ionizing radiation exposure among medical workers: a cohort study of the Canadian National Dose Registry of Radiation Workers. Int J Occup Med Environ Health. 22(2):149-156

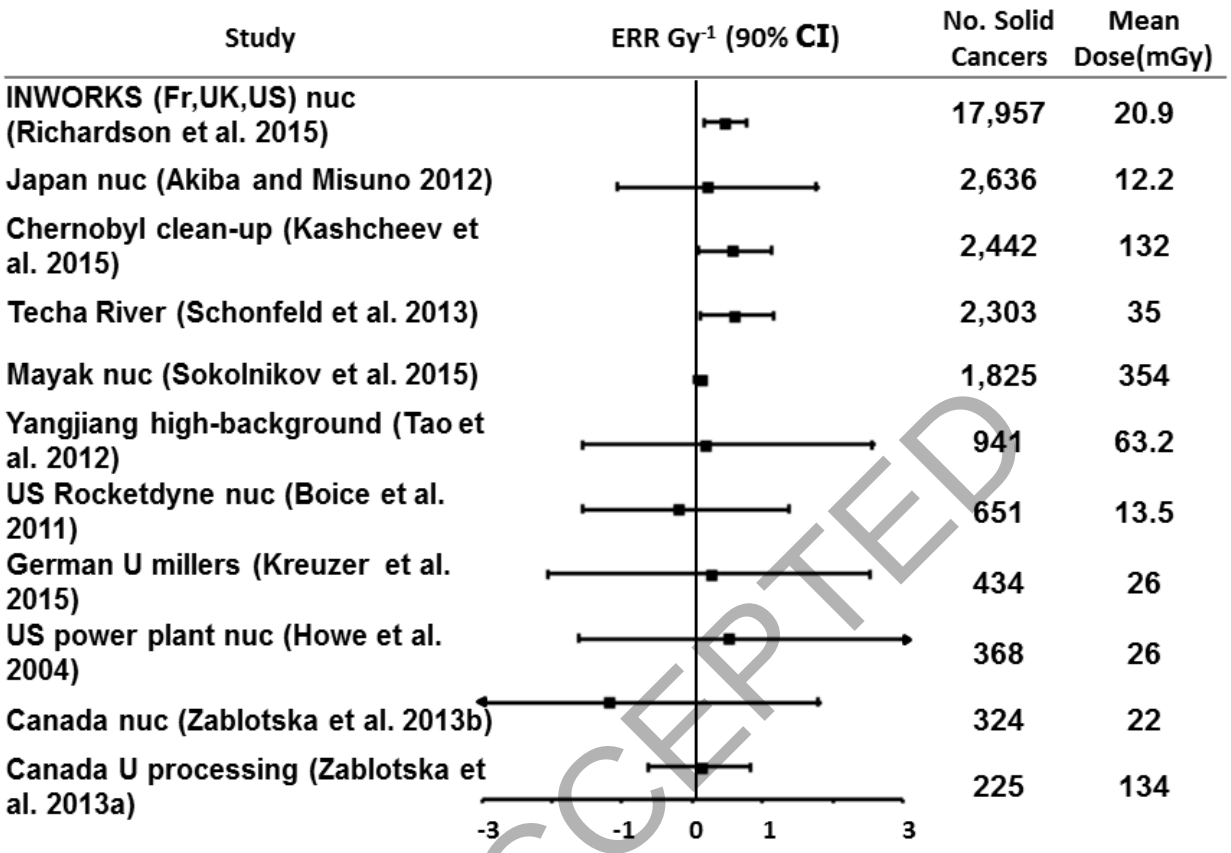
Table 1. Population characteristics for studies of solid cancer mortality (or all non-leukemia mortality) and incidence in cohorts with low dose-rate exposures

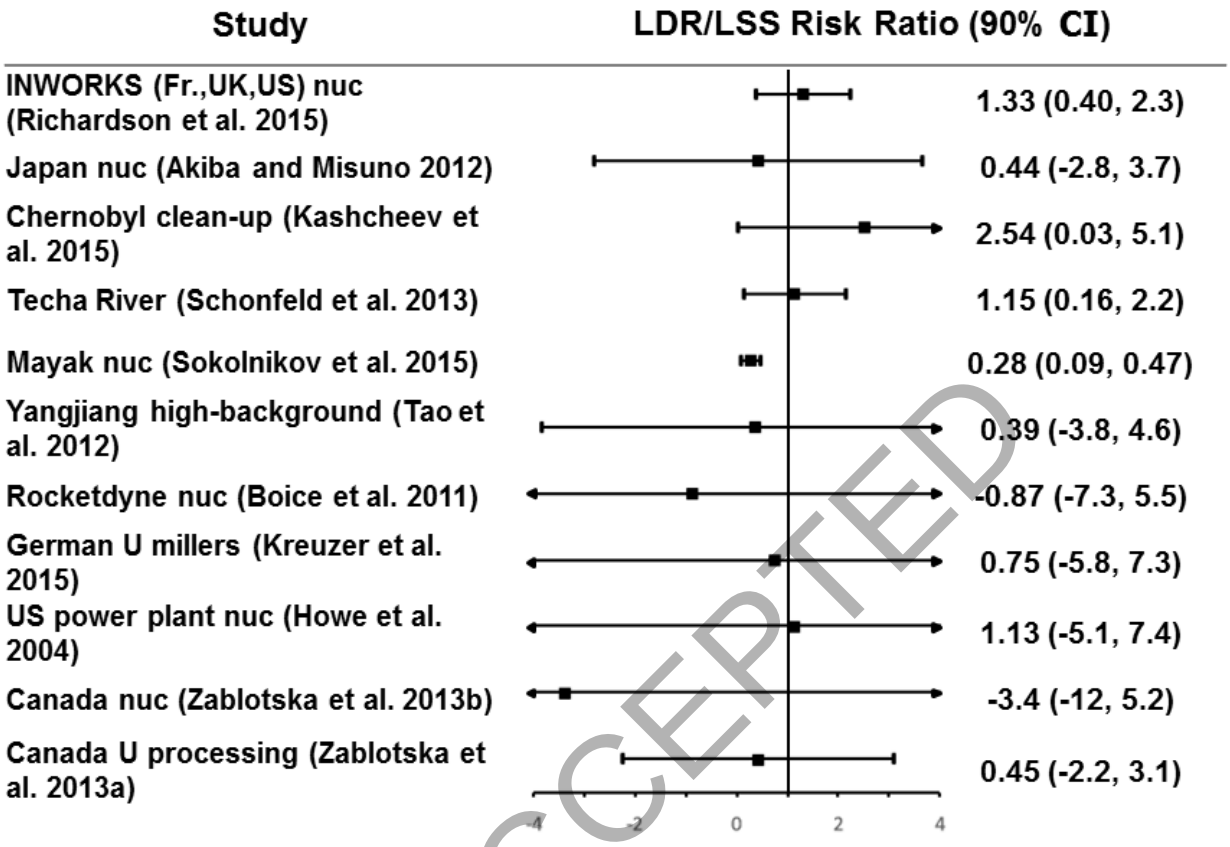
Table 2. Mean doses, numbers of cancers and risk estimates for studies of solid cancer mortality (or all non-leukemia mortality) in cohorts with low dose-rate exposures

Table 3. Sensitivity analyses (results when individual studies are left out) of the mortality data and the mortality+incidence data

Figure 1. Excess relative risk per Gy (ERR Gy^{-1}) in the largest LDR mortality studies (>200 total solid cancer deaths). (Abbreviations: LDR, low dose rate; nuc, nuclear workers; U, uranium)

Figure 2. LDR/LSS risk ratios in the largest LDR studies (>200 total solid cancer deaths), where the LSS risk estimate is matched by sex, age at exposure and attained age to each LDR cohort. (Abbreviations: LDR, low dose rate; LSS, Japanese atomic bomb Life Span Study; nuc, nuclear workers; U, uranium)





Study No.	Study population, Country, Reference	Study characteristics	No. of persons	No. of person-years	Percent females	Average age at start of follow-up (y)[a]	Average length of follow-up (y)
Occupational Radiation Exposures and Mortality							
1	INWORKS, UK, USA, Fr. (Richardson et al. 2015)	Pooled analysis of occupational cohorts, nuclear facilities and NPPs[b]	308,297	8,222,000	13	30.3	26.7
2	Japan, nuclear workers (Akiba and Mizuno 2012)	Nuclear worker registry	200,583	1,373,000	0	31.7	6.8
3	Chernobyl clean-up workers, Russia (Kashcheev et al. 2015)	Chernobyl workers during 1986-87	67,568	993,423	0	34.8	14.7
4	Mayak workers, Russia (Sokolnikov et al. 2015; Sokolnikov et al. 2016)	Weapons production & NPP, external and Pu exposure; risk estimate based on analysis of external exposure	25,757	950,896	25	24.7	36.9
5	Rocketdyne workers, USA (Boice et al. 2011)	Nuclear facility; some internal exposures	5,801	196,674	8	31	33.9
6	Uranium millers, Germany (Kreuzer et al. 2015)	External plus low level radon and uranium exposure; risk estimate	4,054	158,383	0	25	39.1

		based on analysis of external exposure					
7	US, nuclear power plant workers (Howe et al. 2004; Cardis et al. 2007)	NPPs	53,698	698,051	11.9	30.5	14.7
8	Canada, nuclear workers (Zablotska et al. 2013b)	AECL laboratories and NPPs	42,228	514,729	16.8	30.8	12.2
9	Port Hope, Canada uranium workers (Zablotska et al. 2013a)	Radium & uranium processing facility, external plus radon and uranium exposure; risk estimate based on analysis of external exposure	3,000	82,999	11.8	30	27.7
10	Sweden, nuclear workers (Cardis et al. 2007)	Fuel cycle facility and NPP	16,347	220,501	~10	30.6	13.5
11	Germany, NPP workers (Merzenich et al. 2014)	NPPs	8,972	130,737	2.5	35.2	14.6
12	Rocky Flats, USA workers (Cardis et al. 1995)	Nuclear weapons plant, external plus some with Pu exposure	6,638	100,022	0	37	15.1
13	Belgium, nuclear workers (Engels et al. 2005; Cardis et al. 2007)	Nuclear research and fuel cycle, NPPs	5,037	77,246	4.8	28.8	15.3

14	Finland, nuclear workers (Auvinen et al. 2002; Cardis et al. 2007)	NPPs	6,782	90,517	4.6	31.3	13.3
15	Spain, nuclear workers (Cardis et al. 2007)	Nuclear fuel cycle and NPPs	3,633	46,358	~10	31.2	12.8
16	Australia, nuclear workers (Habib et al. 2005; Cardis et al. 2007)	Nuclear research laboratories	877	12,110	27.7	31.2	13.8
17	Slovakia, Jaslovske Bohunice NPP (Gulis 2003)	NPP	2,776	27,991	8.1	28.9	10.1
Environmental Radiation Exposures and Mortality[c]							
18	Techa River, Russia (Schonfeld et al. 2013)	Residents, internal and external environmental exposures	29,730	927,743	58	~28	31.2
19	Yangjiang China, HBRA [d] (Tao et al. 2012)	Residents, lifelong terrestrial external radiation exposures	31,604	736,942	49	31.7	23.3
Radiation Studies with Incidence Data Only							
20	Kerala India, HBRA (Nair et al. 2009)	Residents, lifelong terrestrial external radiation exposures	69,958	736,586	54.1	~47	10.5
21	Taiwan, radiocontaminated dwellings (Hwang et	^{60}Co contaminated dwellings	6,242	118,000	34.4	16.9	18.9

	al. 2008)						
22	Korea, NPP workers (Jeong et al. 2010)	NPPs	8,429	63,503	0	33.8	41.3

[a] For a few studies the mean age at start of follow-up was not reported. If so, an approximation was made based on the age distribution or other information given.

[b] NPP = nuclear power plant

[c] An additional study of those downwind of the Semipalatinsk nuclear bomb testing site (Bauer et al. 2005) is under dosimetry revision so was not considered quantitatively here.

[d] HBRA, high background radiation area

Study Identifiers [a]	Mean reported dose (mGy)	No. of cancers	LDR Study Risk: ERR Gy^{-1} (90% CI)	Corresponding LSS Risk: ERR Gy^{-1} (90% CI)	LDR/LSS: Risk ratio of this study to the LSS (90% CI)
Occupational Radiation Exposures and Mortality					
1 INWORKS	20.9[b1,b6]	17,957[c1]	0.47 (0.18, 0.79)	0.35 (0.26, 0.45)	1.33 (0.40, 2.26)
2 Japan nuc [e]	12.2[b1]	2,636[c3]	0.20 (-1.42, 2.09)[d]	0.46 (0.22, 0.69)	0.44 (-2.81, 3.68)
3 Chernobyl	132[b2]	2,442[c1]	0.58 (0.002, 1.25)[d]	0.23 (0.14, 0.32)	2.54 (0.03, 5.06)
4 Mayak	354[b1]	593 [c4]	0.12 (0.03, 0.21) 0.20 (-0.0002, 0.46) [d,g]	0.43 (0.32, 0.54) 0.43 (0.32, 0.54)	0.28 (0.09, 0.47) 0.47 (0.0006, 0.94) [g]
5 Rocketdyne	13.5[b3]	651 [c2]	-0.2 (-1.8, 1.7)[d]	0.23 (0.17, 0.29)	-0.87 (-7.27, 5.53)
6 U millers	26[b3]	434 [c1]	0.26 (-2.47, 2.99)[d]	0.36 (0.26, 0.45)	0.75 (-5.82, 7.32)
7 US NPPs	25.7[b1]	368 [c1]	0.51 (-2.01, 4.64)[d]	0.45 (0.29, 0.61)	1.13 (-5.14, 7.41)
8 Canada nuc	21.6[b3]	324[c1]	-1.2 (-4.79, 2.39)[d,f]	0.36 (0.22, 0.49)	-3.38 (-11.9, 5.20)
9 Port Hope	134[b3]	225[c1]	0.12 (-0.74, 0.98) [d,f]	0.27 (0.20, 0.34)	0.45 (-2.23, 3.12)
10 Sweden nuc	6.1[b3]	190 [c2]	-0.58 (-7.65, 6.49) [f]	0.34 (0.22, 0.46)	-1.71 (-22.6, 19.2)
11 Germany NPPs	29.5[b4]	115[c1]	-0.98 (-3.98, 1.02)	0.32 (0.19, 0.44)	-3.21 (-11.3, 4.91)
12 Rocky Flats	36.4[b5]	104 [c2]	-1.63 (-3.76, 0.5)	0.28 (0.17, 0.40)	-5.73 (-13.5, 2.08)
13 Belgium nuc	26.6[b3]	87 [c2]	-0.59 (-7.42, 6.24) [f]	0.35 (0.22, 0.48)	-1.68 (-21.1, 17.8)
14 Finland nuc	7.9[b3]	33 [c2]	174 (-720, 1070) [f]	0.32 (0.20, 0.44)	547 (-2279, 3374)
15 Spain nuc	25.5[b3]	25 [c2]	1.02 (-11.9, 13.9) [f]	0.34 (0.21, 0.47)	3.01 (-35.0, 41.0)
16 Australia nuc	6.1[b3]	17 [c2]	13.4 (-6.0, 119)	0.38 (0.26, 0.51)	34.9 (-128, 198)
17 Slovakia nuc	1.91[b3]	10 [c2]	9.5 (-60, 36)[d]	0.40 (0.23, 0.57)	23.7 (-77.4, 125)
Environmental Radiation Exposures and Mortality					
18 Techa River	35[b5]	2,303[c1]	0.61 (0.04, 1.27)[d]	0.53 (0.44, 0.61)	1.15 (0.16, 2.15)
19 Yangjiang HBRA[h]	63.2[b1]	941[c5]	0.19 (-1.87, 3.04)[d]	0.49 (0.37, 0.61)	0.39 (-3.82, 4.59)
Radiation Exposures, with Incidence Data Only					
20 Kerala HBRA	161[b3]	1,349 [c2]	-0.13 (-0.58, 0.46)[d]	0.34 (0.24, 0.43)	-0.39 (-1.69, 0.92)

21 Taiwan dwellings	47.7[b3]	106 [c1]	0.3 (-0.4, 0.9)	1.24 (0.96, 1.53)	0.24 (-0.28, 0.77)
22 Korea NPP	19.7[b3]	96[c2]	2.06 (-1.91, 9)[d]	0.56 (0.37, 0.74)	3.70 (-4.61, 12.0)

[a] The study numbers correspond to those in Table 1, where references are given.

[b] Reported dose: [b1] Colon dose, [b2] Skin dose, [b3] Described as whole-body or Hp(10) dose, [b4] "Effective dose", [b5] Stomach dose, [b6] Mean dose among only those with "positive recorded dose".

[c] Reported cancer endpoint: [c1] All solid cancers, [c2] All cancers except leukaemia, [c3] Excluding leukaemia and alcohol-related cancers (oropharynx, oesophagus and liver), [c4] Solid cancers except liver, lung, bone, [c5] All solid cancers except liver.

[d] 95% CI.

[e] "nuc": nuclear workers

[f] Lower confidence bound not estimated in original paper. Estimated here by assuming arithmetic symmetry of the upper and lower bounds around the point estimate.

[g] The first line gives the risk estimate for all Mayak workers, adjusting statistically for ^{239}Pu exposure; second line is for workers at Mayak plants with little potential for Pu exposure (excluding the Pu and radiochemical plants).

[h] HBRA, high background radiation area

	Meta-analysis Weight (%) for the Study Being Deleted [A]	Ratio of LDR to LSS Risk: Ratio (95% CI)
<u>Part A:</u> Sensitivity Analyses Using the Full Mayak Cohort and the INWORKS Study		
Mortality: All studies included [B]		***0.36 (0.14, 0.57)***
Mayak (full cohort) excluded	91.0	1.12 (0.40, 1.84)
INWORKS excluded	3.8	0.32 (0.10, 0.54)
Techa River excluded	3.3	0.33 (0.11, 0.55)
Mortality+Incidence: All studies included		***0.33 (0.13, 0.54)***
Mayak excluded	79.8	0.54 (0.09, 0.99)
Taiwan exposed residents excluded	10.5	0.34 (0.13, 0.56)
INWORKS excluded	3.3	0.30 (0.09, 0.51)
Techa excluded	2.9	0.31 (0.10, 0.51)
<u>Part B:</u> Sensitivity Analyses Using the non-Plutonium Part of the Mayak Cohort		
Mortality: All studies included		***0.71 (0.27, 1.15)***
Mayak excluded	62.6	1.12 (0.40, 1.84)
INWORKS excluded	15.7	0.60 (0.12, 1.08)
Techa excluded	13.8	0.64 (0.17, 1.12)
Chernobyl cleanup workers excluded	2.2	0.67 (0.22, 1.12)
Mortality+Incidence: All studies included		***0.51 (0.16, 0.86)***
Mayak (non-Pu cohort) excluded	39.7	0.54 (0.09, 0.99)
Taiwan exposed residents excluded	31.4	0.63 (0.21, 1.06)
INWORKS excluded	10.0	0.42 (0.05, 0.79)

Techa River excluded	8.7	0.45 (0.08, 0.82)
Kerala excluded	5.1	0.56 (0.20, 0.92)

[A] Only studies with a meta-analysis weight (percentage of the total variance accounted for) of at least 2% are shown. Those with <2% weight had trivial effects upon the risk ratio estimate.

[B] For each section the meta-analytic ERR Gy^{-1} for all the relevant studies is given first, for comparison with the ERRs when individual studies are excluded.