Published in final edited form as:

Radiat Environ Biophys. 2013 November ; 52(4): 435–449. doi:10.1007/s00411-013-0484-7.

A Review of Non-Cancer Effects, Especially Circulatory and Ocular Diseases¹

Mark P. Little

Radiation Epidemiology Branch, National Cancer Institute, 9609 Medical Center Drive MSC 9778, Bethesda, MD 20892-9778 USA

Mark P. Little: mark.little@nih.gov

Abstract

There is a well-established association between high doses (> 5 Gy) of ionizing radiation exposure and damage to the heart and coronary arteries, although only recently have studies with high quality individual dosimetry been conducted that would enable quantification of this risk adjusting for concomitant chemotherapy. The association between lower dose exposures and late occurring circulatory disease has only recently begun to emerge in the Japanese atomic bomb survivors and in various occupationally-exposed cohorts, and is still controversial. Excess relative risks per unit dose in moderate and low dose epidemiological studies are somewhat variable, possibly a result of confounding and effect modification by well known (but unobserved) risk factors.

Radiation doses of 1 Gy or more are associated with increased risk of posterior subcapsular cataract. Accumulating evidence from the Japanese atomic bomb survivors, Chernobyl liquidators, US astronauts and various other exposed groups suggest that cortical cataracts may also be associated with ionizing radiation, although there is little evidence that nuclear cataracts are radiogenic. The dose response appears to be linear, although modest thresholds (of no more than about 0.6 Gy) cannot be ruled out.

A variety of other non-malignant effects have been observed after moderate/low dose exposure in various groups, in particular respiratory and digestive disease and central nervous system (and in particular neuro-cognitive) damage. However, because these are generally only observed in isolated groups, or because the evidence is excessively heterogeneous, these associations must be treated with caution.

Keywords

circulatory disease; radiation; heart disease; stroke; cataract; central nervous system; review

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 (Committee to Assess

¹This article is based on a talk with the title “Non-cancer effects, especially circulatory diseases” that was presented as an invited paper at the IRPA 13th International Congress of the International Radiation Protection Association, Glasgow 13–18 May 2012.

Health Risks from Exposure to Low Levels of Ionizing Radiation 2006; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008a). In particular, leukemia was the first cancer type to be observed in excess among the survivors of the atomic bombings of Hiroshima and Nagasaki (Folley *et al.* 1952). Most other cancer types have been associated with radiation exposure, whether in the Japanese atomic bomb survivors (Ozasa *et al.* 2012; Preston *et al.* 2007) or in other groups (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008a). At high radiation doses (> 5 Gy) 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. A number of recent systematic reviews have presented evidence suggesting an excess radiation-induced risk at occupational and environmental dose levels (< 0.5 Gy²) (Advisory Group on Ionising Radiation 2010; Little *et al.* 2008; Little *et al.* 2010; Little *et al.* 2012a; McGale and Darby 2005; McGale and Darby 2008; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008b) although the presence and magnitude of low-dose risk is still unclear, with some advocating use of a threshold (International Commission on Radiological Protection 2012; Schöllnberger *et al.* 2012).

For some time it has been known that radiation doses of 1 Gy or more could induce posterior subcapsular cataract (PSC) (Edwards and Lloyd 1998). There is accumulating evidence from the Japanese atomic bomb survivors (Minamoto *et al.* 2004; Neriishi *et al.* 2012), Chernobyl liquidators (Worgul *et al.* 2007), US astronauts (Chylack *et al.* 2009) and various other exposed groups, reviewed by Ainsbury *et al.* (Ainsbury *et al.* 2009) and Hammer *et al.* (Hammer *et al.* 2013), to suggest that cortical cataracts (CC) may also be associated with ionizing radiation exposure; there is little evidence that nuclear cataracts (NC) are radiogenic.

Here, we briefly summarize the evidence for a causal association between moderate-and low-level radiation exposure (whether at high or low dose rates) and these various types of non-malignant diseases, with special focus on cardiovascular disease, because of its potential impact on radiation detriment. This paper does not, unlike some previous reviews (Little *et al.* 2008; Little *et al.* 2010; Little *et al.* 2012a; McGale and Darby 2005), aim to be a systematic review, either in relation to circulatory or other diseases, but does augment these previous reviews of radiation-associated circulatory disease, as also of cataract (Ainsbury *et al.* 2009; Hammer *et al.* 2013) with the known literature.

Results

Review of the epidemiological data for circulatory disease

There are multiple types of circulatory disease, and the list given in Table 1 is not exhaustive. Damage to the vasculature can affect the function of most body organs through restriction of blood flow and oxygen to tissue; however, it is mainly the heart and brain that are of concern. At high radiation doses (organ doses > 5 Gy), such as would be received by patients treated with radiotherapy (RT), a variety of adverse effects in the circulatory system

²The equivalent dose, in sievert (Sv), with different types of radiation absorbed dose weighted by their biological effectiveness at inducing stochastic effects, is numerically very close to the (unweighted) absorbed dose, in gray (Gy), for all studies considered here.

have been noted, among them damage to the structures of the heart – including marked diffuse fibrotic damage, especially of the pericardium and myocardium, pericardial adhesions, microvascular damage and stenosis of the valves – and to the coronary, carotid and other large arteries; these sorts of damage occur both in patients receiving RT 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).

Findings in the Japanese atomic bomb survivors—Excess radiation-associated mortality due to heart disease and stroke has been observed in the Life Span Study (LSS) cohort (Table 2) (Shimizu *et al.* 2010). In the latest follow-up of the Adult Health Study (AHS) Yamada *et al.* (Yamada *et al.* 2004) observed generally non-statistically significant radiation-associated excess risks for incidence of hypertension and myocardial infarction (Table 2). A study within the AHS of those exposed in early childhood showed a significantly increased incidence of non-fatal stroke or myocardial infarction, although there was no excess risk among those exposed *in utero* for whom the average exposures were much lower (Tatsukawa *et al.* 2008) (Table 2). The studies of Yamada *et al.* (Yamada *et al.* 2004) and Tatsukawa *et al.* (Tatsukawa *et al.* 2008) were the only epidemiological reports apart from those of Ivanov *et al.* (Ivanov *et al.* 2006) and Azizova *et al.* (Azizova *et al.* 2010a; Azizova *et al.* 2010b) to have assessed morbidity rather than mortality.

Some aspects of the Japanese atomic bomb survivor data imply that risks may not necessarily apply to other exposed populations. The atomic bomb survivors suffered from burns, epilation and other acute injuries caused by the radiation, heat and blast of the bombs, respectively, and these injuries, in addition to radiation, may have contributed to development of non-cancer diseases in later life. It is possible that as well as the direct effect of the injuries, these and other trauma would introduce a measure of selection, and some evidence of this has been presented by Stewart and Kneale (Stewart and Kneale 2000), who documented evidence of heterogeneity of risk for various endpoints, in particular cardiovascular disease mortality, among the various acute injury groups. However, Stewart and Kneale (Stewart and Kneale 2000) did not consider the effects of dose error – if analysis is conducted taking this into account the evidence for differential effect among those survivors, in particular for cardiovascular disease, was much reduced, and generally not statistically significant (Little 2002). Although selection cannot be entirely discounted, the general consistency of risks in the Japanese and other groups (Table 2) (for a more formal analysis see also (Little *et al.* 2012a)) suggests that it does not have a major impact.

The Japanese survivors were also subject to other privations to be expected of a wartime population, and in particular may have been somewhat malnourished. Malnutrition in early stage of life has been reported to be associated with development of cardiovascular diseases and other disease in later stage of life (Gluckman *et al.* 2007). In malnourished animals, elastin content in the aorta is reportedly reduced (Skilton *et al.* 2006), which could induce arteriosclerosis. Whether for this reason, or because of more direct radiation effects, a dose-dependent increase of aortic calcification has been reported in the Japanese atomic bomb survivors (Yamada *et al.* 2005). However, it would not be expected that malnutrition would be correlated with dose, and so the scope for confounding within the Japanese cohort would

be expected to be slight. As above, the consistency of risks between the Japanese atomic bomb survivors and other exposed groups suggests that there is little effect of malnutrition on the dose response.

Occupationally exposed groups—There were increasing trends with dose for certain circulatory disease mortality endpoints (all circulatory disease, cerebrovascular disease, other circulatory diseases), and decreasing trends for certain other endpoints (ischaemic heart disease (IHD), heart failure, deep vein thrombosis and pulmonary embolism) in the IARC 15-country study of radiation workers (Vrijheid *et al.* 2007) (Table 2), although none were statistically significant (1-sided $p = 0.20$). Radiation-associated excess IHD and stroke morbidity were observed in a group of Chernobyl recovery workers, although there was no increased morbidity due to hypertensive heart disease and other heart disease (Ivanov *et al.* 2006) (Table 2). A highly statistically significant trend with dose was seen for IHD and cerebrovascular disease in the latest analysis of circulatory disease morbidity and mortality in the Mayak workers (Azizova *et al.* 2010a; Azizova *et al.* 2010b). The study is unusual in that doses to certain internal organs, in particular the lung and liver, were dominated by doses from internally deposited radionuclides, in particular the α -particle emitting radioisotopes of plutonium. Doses in this study were among the highest considered here, and arguably were sufficiently high that this study should be considered outside the scope of the review: average whole body doses for external γ rays were 0.83 Gy, with a range of 0 – 5.92 Gy. However, unlike the partial-body doses received from radiotherapy, the external whole-body doses received by the Mayak workers were, in general, accumulated over a protracted period, so it is reasonable to include this population in the present study. Nonetheless, interpretation is complicated by the large and highly heterogeneous internal α -particle dose from plutonium. There was a significant dose response both in relation to external γ dose and internal (α -particle) dose to the liver (Azizova *et al.* 2010a; Azizova *et al.* 2010b). There are few cohorts of sufficient size apart from this with α -particle liver dose; for example individual α -particle liver dose was generally not evaluated in persons exposed to the diagnostic contrast medium Thorotrast (Travis *et al.* 2003).

A borderline significant trend with dose was seen for circulatory disease mortality in the latest analysis of the UK NRRW (Muirhead *et al.* 2009), an excess relative risk (ERR) of 0.25 Sv^{-1} (95% CI $-0.01, 0.54$). In most other workforces (Kreuzer *et al.* 2006; Kreuzer *et al.* 2013; Lane *et al.* 2010; Laurent *et al.* 2010) there were generally no statistically significant trends of circulatory disease with dose (Table 2). It should be noted that these studies overlap, and in particular there is substantial inclusion of the study populations of Muirhead *et al.* (Muirhead *et al.* 2009) within that of the IARC study (Vrijheid *et al.* 2007).

A study of a cohort of environmentally-exposed individuals in the Southern Urals reported a statistically significant, or borderline significant, increase (depending on the latent period used) of both all circulatory disease mortality, with an ERR of 0.24 Gy^{-1} (95% CI $-0.08, 0.59$), and IHD mortality, with an ERR of 0.40 Gy^{-1} (95% CI $-0.11, 0.99$) (with a 10 year lag); the trends were statistically significant ($p = 0.05$) with lags of 15–20 years, but not ($p > 0.1$) with lags of 0–10 years (Krestinina *et al.* 2013). Grosche *et al.* (Grosche *et al.* 2011) studied circulatory disease mortality in a Kazakh group exposed to fallout from nuclear weapons tests at the Semipalatinsk site. No excess circulatory disease risk was reported

within the group of exposed settlements, with an ERR of 0.02 Gy^{-1} (95% CI $-0.32, 0.37$) for cardiovascular disease, an ERR of 0.06 Gy^{-1} (95% CI $-0.39, 0.52$) for heart disease, and an ERR of -0.06 Gy^{-1} (95% CI $-0.65, 0.54$) for stroke; on the other hand, if exposed and unexposed settlements were analyzed together the excess risks were highly statistically significant and implausibly large. The dosimetry in this cohort is problematic, being based on assessments of residence, combined with estimates of time based outdoors and dietary consumption compiled by interview many years (>30) after the bomb tests. As such, the results of this study are largely uninformative.

Radiation-associated excess relative risk for circulatory disease 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 there are borderline significant decreasing trends with attained age (Little *et al.* 2012a; Shimizu *et al.* 2010); increasing time trends have been observed in other groups (Vrijheid *et al.* 2007).

Review of the epidemiological data for cataracts

The lens is an optically clear, avascular tissue that receives nourishment from its surrounding aqueous and vitreous fluids (Harding and Crabbe 1984). Lens transparency depends on the proper differentiation of lens fibre cells from a proliferating subset of a single layer of epithelial cells on the lens anterior surface. Throughout life, epithelial cells located at the periphery of the lens, in the germinative zone, divide and differentiate into mature lens fibre cells. These terminally differentiated cells do not contain nuclei or mitochondria, and are dependent on the overlying epithelial cell layer for nutrient transport, energy production, and protection from insulting agents. While this process slows considerably during puberty, the lens continues to grow throughout life, eventually tripling in weight (Kleiman and Worgul 1994). Due to the unique anatomy of the lens, disruption of the integrity of the epithelial cell layer is likely to lead to cataract (Cogan *et al.* 1952; Von Sallmann 1957; Worgul *et al.* 1989).

From early in embryogenesis, lens growth is entirely determined by proliferation of a small band, approximately 60 cells wide, in an area of the anterior epithelium near the lens equator termed the germinative zone. The mitotic index of cells more anterior to this region, in the central zone, is negligible (McAvoy 1978; Von Sallmann *et al.* 1962), but these cells in the central zone play an important role in maintaining lens metabolism and homeostasis (Kuck 1970). Following terminal cell division, cells in the germinative zone migrate towards the equator and queue up in precise registers called meridional rows. There, they begin to differentiate into mature lens fibre cells.

The principal pathology of the lens is its opacification, termed 'cataract' in its advanced stages (van Heyningen 1975). There are three predominant forms of cataract depending on their anatomical location in the lens: cortical cataract (CC), involving the outer, more recently formed lens fibre cells; nuclear cataract (NC), developing first in the inner embryological and fetal lens fibre cells; and PSC, developing from the dysplasia of transitional zone epithelial cells and resulting in an opacity at the posterior pole (Kuszak and Brown 1994).

For some time it has been known that radiation doses of 1 Gy or more could induce PSC (Edwards and Lloyd 1998). There is accumulating evidence for cataract induction at somewhat lower levels of radiation dose. Studies of the atomic bomb survivors found mixed evidence of a possible threshold for cataract. For example Nakashima *et al.* (Nakashima *et al.* 2006) found a best estimate of 0.6 Sv (90% CI <0, 1.2) for CC and 0.7 (90% CI <0, 2.8) for PSC (Table 3). However, although the central threshold estimate for all surgically removed cataracts in this cohort are not very different, they are generally statistically significant, e.g., using an ERR model the threshold estimate is 0.50 Gy (95% CI 0.10, 0.95) (Neriishi *et al.* 2012) (Table 3). Moreover, there was no evidence for curvature using a linear-quadratic model ($p=0.34$). Estimated thresholds for various cataract endpoints in a cohort of Chernobyl liquidators (Worgul *et al.* 2007) were in the range 0.34–0.50 Gy, with lower 95% CI in the range 0.17–0.19 Gy, and upper 95% CI in the range 0.51–0.69 Gy (Table 3).

Table 4 demonstrates that there is a fair degree of consistency in the radiogenic risks of PSC and CC if continuous dose-response models are fitted. For example, trends of excess odds ratio (EOR) of 0.30 Sv^{-1} (95% CI 0.10, 0.53) were seen for CC and 0.44 Sv^{-1} (95% CI 0.19, 0.73) for PSC (Nakashima *et al.* 2006) (Table 4); for surgically removed cataracts an EOR of 0.32 Gy^{-1} (95% CI 0.17, 0.52) was observed (Neriishi *et al.* 2012) (Table 4). Very similar estimates are derived for these two cataract endpoints in a cohort of Chernobyl liquidators (Worgul *et al.* 2007) (Table 4), and in a group of persons treated for haemangioma in childhood (Hall *et al.* 1999). In contrast, estimates for NC are generally not statistically significant – for example in the atomic bomb survivors the estimated trend of EOR was 0.07 Sv^{-1} (95% CI –0.11, 0.30) (Nakashima *et al.* 2006), and a similar trend of EOR of 0.07 Gy^{-1} (95% CI –0.44, 1.04) was reported in Chernobyl liquidators (Worgul *et al.* 2007). In various other groups (Chodick *et al.* 2008; Mrena *et al.* 2011) somewhat larger risks are observed, although these are generally non-significant; one exception is a study of Icelandic airline pilots that indicated a very large (and borderline significant) risk for NC (Rafnsson *et al.* 2005), with an EOR of 20 Gy^{-1} (95% CI 0, 30).

Although not presented in the Tables 3, 4 because of lack of adequately quantitative and comparable data, there are indications of radiation-associated cortical opacifications in a small group of US astronauts exposed to doses up to about 300 mSv (Chylack *et al.* 2012).

There is epidemiological (Delcourt *et al.* 2005; Zoric *et al.* 2008) and experimental (Devi *et al.* 1965) evidence that cataract may be associated with malnutrition, and so may be implicated in a proportion of the cataracts in the Japanese atomic bomb survivors. However, as above, it would not be expected that malnutrition would be correlated with dose in this group, and so the scope for confounding within the Japanese cohort would be expected to be slight.

Review of other non-malignant endpoints

This has been the subject of a recent review (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008b). The atomic bomb survivor data suggest that there is significant excess risk for non-malignant respiratory and digestive diseases (Ozasa *et al.* 2012). Hall *et al.* (Hall *et al.* 2004) observed cognitive impairment in a

Swedish group treated for haemangioma in infancy with much lower doses, with ~50% reduction in high school attendance associated with >100 mGy exposure; there were similar dose-related reductions in cognitive test performance. A study in an Israeli group treated for ringworm of the scalp in childhood did not suggest any elevated risk of schizophrenia (Sadetzki *et al.* 2011). A Danish study of childhood cancer survivors suggested an elevated excess risk of schizophrenia (Ross *et al.* 2003), but the fact that risk was confined to survivors of brain tumour suggests that it may not necessarily reflect the effects of the treatment received. There is no radiation dosimetry in this study, and nor is there in the study of Imamura *et al.* (Imamura *et al.* 1999), which suggested that prenatal exposure to the effects of the atomic bomb in Nagasaki may be associated with schizophrenia.

Otake and Schull (Otake and Schull 1993) documented radiation-associated small head size among those exposed *in utero* to the atomic bombs in Hiroshima and Nagasaki. There are also radiation-associated reductions of intelligence quotient (IQ) and increase in severe mental retardation, particularly among those *in utero* survivors exposed 8–25 weeks after ovulation (Otake and Schull 1998). There is epidemiological evidence that cognitive defects may be associated with malnutrition (Grantham-McGregor 1995), and so may be implicated in a proportion of this endpoint documented in the Japanese atomic bomb survivors. There is evidence of an inverse correlation of dose with standing height among the *in utero* exposed (Nakashima *et al.* 1995); it is possible that this reflects some correlation of dose with nutritional status, although a direct effect is perhaps more likely. On this interpretation, malnutrition would not appear to be correlated with dose in this group, and so the scope for confounding within the Japanese cohort would be expected to be slight.

Discussion and conclusions

Circulatory disease

We reviewed evidence of elevated risk for various subtypes of circulatory disease in people exposed to low and moderate doses of radiation (mean dose < 0.5 Gy). This is broadly consistent with the findings of previous meta-analyses of this endpoint (Advisory Group on Ionising Radiation 2010; Little *et al.* 2008; Little *et al.* 2010; Little *et al.* 2012a; McGale and Darby 2005; McGale and Darby 2008; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008b). For example, the systematic review and meta-analysis of Little *et al.* (Little *et al.* 2012a) documented statistically significant ERR per unit dose coefficients for the four major subtypes of circulatory disease (IHD, heart disease apart from IHD, stroke, all other circulatory disease) in people exposed to radiation. For ischemic and non-ischemic heart disease, there was no significant heterogeneity in risks between the various studies; however, this was not the case for stroke and other circulatory diseases (Little *et al.* 2012a). Note that a formal meta-analysis was not conducted here; however, there are only three new studies not considered in the earlier review, of the Techa River cohort (Krestinina *et al.* 2013), of the German uranium miner cohort (Kreuzer *et al.* 2013), and of the Semipalatinsk atomic test cohort (Grosche *et al.* 2011), all of which yield risk estimates which are not inconsistent with those previously evaluated (Little *et al.* 2012a), so that the results had these studies been included would almost certainly have been the same.

With the exception of the study of Talbott *et al.* (Talbott *et al.* 2003) and Krestinina *et al.* (Krestinina *et al.* 2013) all circulatory disease studies considered here are either of the Japanese atomic-bomb survivors, or of occupationally exposed groups. All occupational groups are to some extent selected, in that they must be sufficiently fit to be employed as radiation workers. The degree of selection 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 discussed above, Stewart and Kneale (Stewart and Kneale 2000), presented evidence of heterogeneity of risk of cardiovascular disease mortality among various acute injury groups, and suggested that this provided evidence of selection in the atomic bomb survivors. However, analysis that took account of errors in the radiation dose estimates yielded much reduced, and generally statistically non-significant elevations in risk of cardiovascular disease among survivors with acute injuries (Little 2002). 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 likely to be correct, however, for occupationally-exposed groups with a similar degree of selection as those considered here.

The candidate biological mechanisms for the circulatory disease effects of radiation have been recently reviewed (Advisory Group on Ionising Radiation 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 (<0.5 Gy) 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 or moderate dose (mean < 0.5 Gy) from low linear energy transfer radiation in the cohorts analyzed here is uninformative as to specific target tissues, so these remain 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.* 2009); however, this mechanism remains speculative.

In their reviews, Little *et al.* (Little *et al.* 2008; Little *et al.* 2010) document abundant radiobiological reasons for considering the studies of moderate and low doses separately from studies of high doses because the mechanisms relevant for doses in this range are likely to differ from those relevant at higher (e.g., radiotherapeutic) doses.

However, risks in studies of medically-exposed groups, with relevant organ doses usually well above 0.5 Gy, are generally consistent with those in populations exposed at the much lower doses and dose rates discussed above (Darby *et al.* 2013; Little *et al.* 2012a; Little *et al.* 2012b; Little *et al.* 2013b; Mulrooney *et al.* 2009; Tukenova *et al.* 2010), suggesting that mechanisms may be similar at high doses and high dose rates as at low. The consistency of risks of IHD in relation to mean heart dose in these high-dose/partial-body exposed groups, with the risks in the generally uniformly whole-body-exposed groups in relation to whole-body dose discussed above (Table 2), also suggests that mean dose to the heart is the most relevant metric for predicting radiation-associated IHD (Little *et al.* 2013b).

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 independently of the above factors. A particular limitation of most of the studies that are considered here is the absence of information on lifestyle factors. 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 International Commission on Radiological Protection (ICRP) has classified circulatory disease as a tissue reaction (or deterministic) effect (International Commission on Radiological Protection 2012), with a threshold dose of 0.5 Gy. Schöllnberger *et al.* (Schöllnberger *et al.* 2012) present analysis of the older LSS mortality data (based on Preston *et al.* (Preston *et al.* 2003)) and conclude that for cerebrovascular disease, risk estimates are compatible with no risk below a threshold dose of 0.62 Gy, while for cardiovascular disease, risk estimates are consistent with no risk below a threshold dose of 2.19 Gy. Schöllnberger *et al.* (Schöllnberger *et al.* 2012) suggest a novel method for assessing low dose circulatory disease risk based on the established statistical technique of multi-model inference (MMI) (Burnham and Anderson 1998; Claeskens and Hjort 2008), used also in other contexts. Although not explicitly Bayesian, MMI is somewhat related to Bayesian model-averaging and similar Bayesian techniques (Wang *et al.* 2012); these Bayesian methods have the advantage of assessing the parameter uncertainty distribution more thoroughly; it may be judged that the method of Schöllnberger *et al.* does not adequately assess the uncertainties in model parameters, which Bayesian techniques can better address (Wang *et al.* 2012). Moreover, it is doubtful that models incorporating thresholds as employed by Schöllnberger *et al.* (Schöllnberger *et al.* 2012) should be fitted to the Japanese atomic bomb survivor Life Span Study (LSS) cohort's circulatory disease endpoints or any other data of this sort, as discussed elsewhere (Little *et al.* 2013a). There are other aspects of the analysis of Schöllnberger *et al.* (Schöllnberger *et al.* 2012) that are also controversial (Little *et al.* 2013a; Schöllnberger *et al.* 2013).

Cataract

There is reasonably consistent evidence of excess risk of both PSC and CC associated with radiation exposure. In general NC appears not to be radiation related. A curious feature of the Japanese atomic bomb survivor data is that while there appears to be evidence of a significant (i.e., non-zero) threshold, there is no evidence of linear-quadratic curvature in the dose response (Neriishi *et al.* 2012). There is also evidence of a significant threshold for various cataract endpoints in a cohort of Chernobyl liquidators (Worgul *et al.* 2007) (Table 3). The authors also attempted to evaluate curvature using a conventional linear-quadratic model, which yielded little evidence of the upward curvature one would expect if a linear-threshold model were valid (Worgul *et al.* 2007). In other cohorts threshold models do not appear to have been fitted. There are well known methodological problems with fitting of threshold models. The resulting likelihood functions are not C^2 in the model parameters, a sufficient (if not necessary) condition to justify the asymptotic convergence of the likelihood-ratio test and other statistical tests (Schervish 1995), so that all likelihood-based p -values and confidence intervals may be incorrect. The discrepancy between the results of fitting threshold and linear-quadratic models to these two datasets (Neriishi *et al.* 2012; Worgul *et al.* 2007) strongly suggests that this is the case. The ICRP has classified cataract disease as a tissue reaction (or deterministic) effect (International Commission on Radiological Protection 2012), with a threshold dose of 0.5 Gy. As can be seen from Table 3, this is bordering on inconsistency with the findings in a number of datasets, in particular the Chernobyl liquidators (Worgul *et al.* 2007).

There is a fair degree of consistency in the radiogenic risks of PSC and cortical cataracts if continuous dose-response models are fitted (Table 4). Very similar estimates are derived for these two cataract endpoints in three different exposed groups (Hall *et al.* 1999; Nakashima *et al.* 2006; Worgul *et al.* 2007), exposed at very different ages, which are also similar to the risks of surgically-removed cataract (Neriishi *et al.* 2012) (Table 4). Risks in various other groups (Chodick *et al.* 2008; Mrena *et al.* 2011) are generally non-significant. The one exceptional study, of Icelandic airline pilots, indicated a large (and borderline significant) risk for NC (Rafnsson *et al.* 2005); the dosimetry in this study is a reconstruction derived from the pilots' flight logs, and may not be as reliable as the dose estimates in the other studies considered here.

There are a number of other studies than those given in Tables 3, 4 in which problems with radiation dosimetry, endpoint, follow-up, or analysis mean that the studies are largely uninformative, in particular various studies of persons exposed to CT scans (Hourihan *et al.* 1999; Klein *et al.* 1993; Klein *et al.* 2000), radiotherapy patients (Wilde and Sjöstrand 1997), Chernobyl-exposed children (Day *et al.* 1995), various groups of military pilots and astronauts (Jones *et al.* 2007; Rastegar *et al.* 2002), a cohort of interventional cardiologists (Ciraj-Bjelac *et al.* 2010), and residents of contaminated buildings (Chen *et al.* 2001; Hsieh *et al.* 2010).

Diabetes, angina, high BMI and cigarette smoking are well established risk factors for cataract (Chodick *et al.* 2008; Neriishi *et al.* 2012; Worgul *et al.* 2007), although there is no suggestion that they confound the radiation dose response in the studies considered here that

collected relevant information (Neriishi *et al.* 2012; Worgul *et al.* 2007). There is evidence of reduction of radiation-induced relative risk of cataract with increasing age at exposure in a number of studies (Hall *et al.* 1999; Neriishi *et al.* 2012).

Other non-malignant endpoints

The atomic bomb survivor data suggest that there is significant excess risk for non-malignant respiratory and digestive diseases (Ozasa *et al.* 2012). However, this is not generally observed in other exposed groups (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008b).

Many studies of childhood cancer survivors (principally of leukaemia) document cognitive impairment associated with high dose cranial irradiation (Syndikus *et al.* 1994). Slightly surprisingly, Hall *et al.* (Hall *et al.* 2004) observed cognitive impairment in a Swedish group treated for haemangioma in infancy with much lower doses, with a ~50% reduction in high school attendance associated with >100 mGy exposure; there were similar dose-related reductions in cognitive test performance. *In utero* exposed Japanese atomic bomb survivor data also suggest cognitive impairment at high dose, but there is no cognitive impairment (e.g., reduction in IQ) in the 0–100 mGy dose range (Otake and Schull 1998; Schull and Otake 1999). It is not clear the extent to which these two datasets are statistically compatible given the different metrics used; even if they were not, the obvious differences between the exposure-age range make meaningful comparisons difficult.

Acknowledgments

This work was supported by the Intramural Research Program of the National Institutes of Health, the National Cancer Institute, Division of Cancer Epidemiology and Genetics. The author is grateful for the detailed and helpful comments of Dr Alice Sigurdson and the two referees.

Reference List

- Adams MJ, Grant EJ, Kodama K, Shimizu Y, Kasagi F, Suyama A, Sakata R, Akahoshi M. Radiation dose associated with renal failure mortality: a potential pathway to partially explain increased cardiovascular disease mortality observed after whole-body irradiation. *Radiat Res.* 2012; 177:220–228. [PubMed: 22149958]
- Adams MJ, Hardenbergh PH, Constine LS, Lipshultz SE. Radiation-associated cardiovascular disease. *Crit Rev Oncol Hematol.* 2003; 45:55–75. [PubMed: 12482572]
- Advisory Group on Ionising Radiation. Report of the independent Advisory Group on Ionising Radiation. Health Protection Agency; Holborn Gate, 330 High Holborn, London: 2010. Circulatory disease risk; p. 1-116.
- Ainsbury EA, Bouffler SD, Dörr W, Graw J, Muirhead CR, Edwards AA, Cooper J. Radiation cataractogenesis: a review of recent studies. *Radiat Res.* 2009; 172:1–9. [PubMed: 19580502]
- Azizova TV, Muirhead CR, Druzhinina MB, Grigoryeva ES, Vlasenko EV, Sumina MV, O'Hagan JA, Zhang W, Haylock RGE, Hunter N. Cardiovascular diseases in the cohort of workers first employed at Mayak PA in 1948–1958. *Radiat Res.* 2010a; 174:155–168. [PubMed: 20681782]
- Azizova TV, Muirhead CR, Druzhinina MB, Grigoryeva ES, Vlasenko EV, Sumina MV, O'Hagan JA, Zhang W, Haylock RGE, Hunter N. Cerebrovascular diseases in the cohort of workers first employed at Mayak PA in 1948–1958. *Radiat Res.* 2010b; 174:851–864. [PubMed: 21128809]
- Burnham, KP.; Anderson, DR. Model selection and multimodel inference: a practical information-theoretic approach. second. New York: Springer; 1998. p. 1-496.

- Burns DM. Epidemiology of smoking-induced cardiovascular disease. *Prog Cardiovasc Dis.* 2003; 46:11–29. [PubMed: 12920698]
- Chen W-L, Hwang J-S, Hu T-H, Chen M-S, Chang WP. Lenticular opacities in populations exposed to chronic low-dose-rate gamma radiation from radiocontaminated buildings in Taiwan. *Radiat Res.* 2001; 156:71–77. [PubMed: 11418075]
- Chodick G, Bekiroglu N, Hauptmann M, Alexander BH, Freedman DM, Doody MM, Cheung LC, Simon SL, Weinstock RM, Bouville A, Sigurdson AJ. Risk of cataract after exposure to low doses of ionizing radiation: a 20-year prospective cohort study among US radiologic technologists. *Am J Epidemiol.* 2008; 168:620–631. [PubMed: 18664497]
- Chylack LT Jr, Feiveson AH, Peterson LE, Tung WH, Wear ML, Marak LJ, Hardy DS, Chappell LJ, Cucinotta FA. NASCA report 2: Longitudinal study of relationship of exposure to space radiation and risk of lens opacity. *Radiat Res.* 2012; 178:25–32. [PubMed: 22687051]
- Chylack LT Jr, Peterson LE, Feiveson AH, Wear ML, Manuel FK, Tung WH, Hardy DS, Marak LJ, Cucinotta FA. NASA study of cataract in astronauts (NASCA). Report 1: Cross-sectional study of the relationship of exposure to space radiation and risk of lens opacity. *Radiat Res.* 2009; 172:10–20. [PubMed: 19580503]
- Ciraj-Bjelac O, Rehani MM, Sim KH, Liew HB, Vano E, Kleiman NJ. Risk for radiation-induced cataract for staff in interventional cardiology: is there reason for concern? *Catheter Cardiovasc Interv.* 2010; 76:826–834. [PubMed: 20549683]
- Claeskens, G.; Hjort, NL. Model selection and model averaging. Cambridge University Press; 2008. p. 1-312. Cambridge Series in Statistical and Probabilistic Mathematics Cambridge
- Cogan DG, Donaldson DD, Reese AB. Clinical and pathological characteristics of radiation cataract. *AMA Arch Ophthalmol.* 1952; 47:55–70. [PubMed: 14884801]
- Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation NRC. Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII – Phase 2. Washington, DC, USA: National Academy Press; 2006. p. 1-406.
- Danesh J, Whincup P, Lewington S, Walker M, Lennon L, Thomson A, Wong Y-K, Zhou X, Ward M. *Chlamydia pneumoniae* IgA titres and coronary heart disease – Prospective study and meta-analysis. *European Heart Journal.* 2002; 23:371–375. [PubMed: 11846494]
- Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, Correa C, Cutter D, Gagliardi G, Gigante B, Jensen M-B, Nisbet A, Peto R, Rahimi K, Taylor C, Hall P. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med.* 2013; 368:987–998. [PubMed: 23484825]
- Day R, Gorin MB, Eller AW. Prevalence of lens changes in Ukrainian children residing around Chernobyl. *Health Phys.* 1995; 68:632–642. [PubMed: 7730059]
- Delcourt C, Dupuy A-M, Carriere I, Lacroux A, Cristol J-P. Albumin and transthyretin as risk factors for cataract: the POLA study. *Arch Ophthalmol.* 2005; 123:225–232. [PubMed: 15710820]
- Devi A, Raina PL, Singh A. Abnormal protein and nucleic acid metabolism as a cause of cataract formation induced by nutritional deficiency in rabbits. *Br J Ophthalmol.* 1965; 49:271–275. [PubMed: 14290874]
- Edwards AA, Lloyd DC. Risks from ionising radiation: deterministic effects. *J Radiol Prot.* 1998; 18:175–183. [PubMed: 9791808]
- Folley JH, Borges W, Yamawaki T. Incidence of leukemia in survivors of the atomic bomb in Hiroshima and Nagasaki, Japan. *Am J Med.* 1952; 13:311–321. [PubMed: 12985588]
- Gluckman PD, Hanson MA, Beedle AS. Early life events and their consequences for later disease: a life history and evolutionary perspective. *Am J Hum Biol.* 2007; 19:1–19. [PubMed: 17160980]
- Grantham-McGregor S. A review of studies of the effect of severe malnutrition on mental development. *J Nutr.* 1995; 125:2233S–2238S. [PubMed: 7542705]
- Grosche B, Lackland DT, Land CE, Simon SL, Apsalikov KN, Pivina LM, Bauer S, Gusev BI. Mortality from cardiovascular diseases in the Semipalatinsk historical cohort, 1960–1999, and its relationship to radiation exposure. *Radiat Res.* 2011; 176:660–669. [PubMed: 21787182]
- Hall P, Adami H-O, Trichopoulos D, Pedersen NL, Ligiou P, Ekblom A, Ingvar M, Lundell M, Granath F. Effect of low doses of ionising radiation in infancy on cognitive function in adulthood: Swedish population based cohort study. *BMJ.* 2004; 328:19. [PubMed: 14703539]

- Hall P, Granath F, Lundell M, Olsson K, Holm L-E. Lenticular opacities in individuals exposed to ionizing radiation in infancy. *Radiat Res.* 1999; 152:190–195. [PubMed: 10409329]
- Hammer GP, Scheidemann-Wesp U, Samkange-Zeeb F, Wicke H, Neriishi K, Blettner M. Occupational exposure to low doses of ionizing radiation and cataract development: a systematic literature review and perspectives on future studies. *Radiat Environ Biophys.* 2013; 52:303–319. [PubMed: 23807741]
- Harding, JJ.; Crabbe, MJC. The eye. In: Davson, H., editor. *The lens: development, proteins, metabolism and cataract*. 3. Orlando, Florida: Academic Press; 1984. p. 207-492.
- Hourihan F, Mitchell P, Cumming RG. Possible associations between computed tomography scan and cataract: the Blue Mountains Eye Study. *Am J Public Health.* 1999; 89:1864–1866. [PubMed: 10589319]
- Hsieh WA, Lin I-F, Chang WP, Chen W-L, Hsu YH, Chen M-S. Lens opacities in young individuals long after exposure to protracted low-dose-rate γ radiation in ^{60}Co -contaminated buildings in Taiwan. *Radiat Res.* 2010; 173:197–204. [PubMed: 20095852]
- Imamura Y, Nakane Y, Ohta Y, Kondo H. Lifetime prevalence of schizophrenia among individuals prenatally exposed to atomic bomb radiation in Nagasaki City. *Acta Psychiatr Scand.* 1999; 100:344–349. [PubMed: 10563451]
- International Commission on Radiological Protection. ICRP statement on tissue reactions and early and late effects of radiation in normal tissues and organs – threshold doses for tissue reactions in a radiation protection context. ICRP publication 118. *Ann ICRP.* 2012; 41(1–2):1–322.
- Ivanov VK, Maksimov MA, Chekin SY, Petrov AV, Biryukov AP, Kruglova ZG, Matyash VA, Tsyb AF, Manton KG, Kravchenko JS. The risk of radiation-induced cerebrovascular disease in Chernobyl emergency workers. *Health Phys.* 2006; 90:199–207. [PubMed: 16505616]
- Jones JA, McCarten M, Manuel K, Djojonegoro B, Murray J, Feiversen A, Wear M. Cataract formation mechanisms and risk in aviation and space crews. *Aviat Space Environ Med.* 2007; 78:A56–A66. [PubMed: 17511300]
- Kleiman, NJ.; Worgul, BV. Duane's Foundations of clinical ophthalmology. In: Tasman, W.; Jaeger, EA., editors. *Lens*. Vol. 1. Philadelphia, PA: JP Lippincott and Co; 1994. p. 1-39.
- Klein BEK, Klein R, Linton KLP, Franke T. Diagnostic x-ray exposure and lens opacities: the Beaver Dam Eye Study. *Am J Public Health.* 1993; 83:588–590. [PubMed: 8460743]
- Klein BEK, Klein R, Moss SE. Exposure to diagnostic x-rays and incident age-related eye disease. *Ophthalmic Epidemiol.* 2000; 7:61–65. [PubMed: 10652172]
- Krestinina LY, Epifanova S, Silkin S, Mikryukova L, Degteva M, Shagina N, Akleyev A. Chronic low-dose exposure in the Techa River Cohort: risk of mortality from circulatory diseases. *Radiat Environ Biophys.* 2013; 52:47–57. [PubMed: 23124827]
- Kreuzer M, Dufey F, Sogl M, Schnelzer M, Walsh L. External gamma radiation and mortality from cardiovascular diseases in the German WISMUT uranium miners cohort study, 1946–2008. *Radiat Environ Biophys.* 2013; 52:37–46. [PubMed: 23192731]
- Kreuzer M, Kreisheimer M, Kandel M, Schnelzer M, Tschense A, Grosche B. Mortality from cardiovascular diseases in the German uranium miners cohort study, 1946–1998. *Radiat Environ Biophys.* 2006; 45:159–166. [PubMed: 16897062]
- Kuck, J. Biochemistry of the eye. In: Graymore, CN., editor. *Metabolism of the lens*. London: Academic Press; 1970. p. 261-318.
- Kusunoki Y, Kyoizumi S, Hirai Y, Suzuki T, Nakashima E, Kodama K, Seyama T. Flow cytometry measurements of subsets of T, B and NK cells in peripheral blood lymphocytes of atomic bomb survivors. *Radiat Res.* 1998; 150:227–236. [PubMed: 9692368]
- Kuszek, JR.; Brown, HG. Principles and practice of ophthalmology: basic sciences. In: Albert, DM.; Jakobiec, FA., editors. *Embryology and anatomy of the lens*. Philadelphia: WB Saunders; 1994. p. 82-96.
- Lane RS, Frost SE, Howe GR, Zablotska LB. Mortality (1950–1999) and cancer incidence (1969–1999) in the cohort of Eldorado uranium workers. *Radiat Res.* 2010; 174:773–785. [PubMed: 21128801]
- Laurent O, Metz-Flamant C, Rogel A, Hubert D, Riedel A, Garcier Y, Laurier D. Relationship between occupational exposure to ionizing radiation and mortality at the French electricity

company, period 1961–2003. *Int Arch Occup Environ Health*. 2010; 83:935–944. [PubMed: 20148259]

- Little MP. Absence of evidence for differences in the dose-response for cancer and non-cancer endpoints by acute injury status in the Japanese atomic-bomb survivors. *Int J Radiat Biol*. 2002; 78:1001–1010. [PubMed: 12456287]
- Little MP. Threshold and other departures from linear-quadratic curvature in the non-cancer mortality dose-response curve in the Japanese atomic bomb survivors. *Radiat Environ Biophys*. 2004; 43:67–75. [PubMed: 15221316]
- Little MP, Azizova TV, Bazyka D, Bouffler SD, Cardis E, Chekin S, Chumak VV, Cucinotta FA, de Vathaire F, Hall P, Harrison JD, Hildebrandt G, Ivanov V, Kashcheev VV, Klymenko SV, Kreuzer M, Laurent O, Ozasa K, Schneider T, Tapio S, Taylor AM, Tzoulaki I, Vandoolaeghe WL, Wakeford R, Zablotska LB, Zhang W, Lipshultz SE. Systematic review and meta-analysis of circulatory disease from exposure to low-level ionizing radiation and estimates of potential population mortality risks. *Environ Health Perspect*. 2012a; 120:1503–1511. [PubMed: 22728254]
- Little MP, Azizova TV, Bazyka D, Bouffler SD, Cardis E, Chekin S, Chumak VV, Cucinotta FA, de Vathaire F, Hall P, Harrison JD, Hildebrandt G, Ivanov V, Kashcheev VV, Klymenko SV, Laurent O, Ozasa K, Tapio S, Taylor AM, Tzoulaki I, Vandoolaeghe WL, Wakeford R, Zablotska L, Zhang W, Lipshultz SE. Comment on “Dose-responses from multi-model inference for the non-cancer disease mortality of atomic bomb survivors” (*Radiat. Environ. Biophys* (2012) 51:165–178) by Schöllnberger *et al*. *Radiat Environ Biophys*. 2013a; 52:157–159. [PubMed: 23296519]
- Little MP, Charles MW. Bomb survivor selection and consequences for estimates of population cancer risks. *Health Phys*. 1990; 59:765–775. [PubMed: 2228606]
- Little MP, Gola A, Tzoulaki I. A model of cardiovascular disease giving a plausible mechanism for the effect of fractionated low-dose ionizing radiation exposure. *PLoS Comput Biol*. 2009; 5:e1000539. [PubMed: 19851450]
- Little MP, Kleinerman RA, Stovall M, Smith SA, Mabuchi K. Analysis of dose response for circulatory disease after radiotherapy for benign disease. *Int J Radiat Oncol Biol Phys*. 2012b; 84:1101–1109. [PubMed: 22494591]
- Little MP, Tawn EJ, Tzoulaki I, Wakeford R, Hildebrandt G, Paris F, Tapio S, Elliott P. A systematic review of epidemiological associations between low and moderate doses of ionizing radiation and late cardiovascular effects, and their possible mechanisms. *Radiat Res*. 2008; 169:99–109. [PubMed: 18159955]
- Little MP, Tawn EJ, Tzoulaki I, Wakeford R, Hildebrandt G, Paris F, Tapio S, Elliott P. Review and meta-analysis of epidemiological associations between low/moderate doses of ionizing radiation and circulatory disease risks, and their possible mechanisms. *Radiat Environ Biophys*. 2010; 49:139–153. [PubMed: 19862545]
- Little MP, Zablotska LB, Lipshultz SE. Ischemic heart disease after breast cancer radiotherapy. *N Engl J Med*. 2013b; 368:2523–2524. [PubMed: 23802524]
- McAvoy JW. Cell division, cell elongation and distribution of α -, β - and γ -crystallins in the rat lens. *J Embryol Exp Morphol*. 1978; 44:149–165. [PubMed: 650132]
- McGale P, Darby SC. Low doses of ionizing radiation and circulatory diseases: a systematic review of the published epidemiological evidence. *Radiat Res*. 2005; 163:247–257. 711. [PubMed: 15733031]
- McGale P, Darby SC. Commentary: A dose-response relationship for radiation-induced heart disease—current issues and future prospects. *Int J Epidemiol*. 2008; 37:518–523. [PubMed: 18450809]
- McGeoghegan D, Binks K, Gillies M, Jones S, Whaley S. The non-cancer mortality experience of male workers at British Nuclear Fuels plc, 1946–2005. *Int J Epidemiol*. 2008; 37:506–518. [PubMed: 18319298]
- Minamoto A, Taniguchi H, Yoshitani N, Mukai S, Yokoyama T, Kumagami T, Tsuda Y, Mishima HK, Amemiya T, Nakashima E, Neriishi K, Hida A, Fujiwara S, Suzuki G, Akahoshi M. Cataract in atomic bomb survivors. *Int J Radiat Biol*. 2004; 80:339–345. [PubMed: 15223766]
- Mitchel RE, Hasu M, Bugden M, Wyatt H, Little MP, Gola A, Hildebrandt G, Priest ND, Whitman SC. Low-dose radiation exposure and atherosclerosis in *ApoE*^{−/−} mice. *Radiat Res*. 2011; 175:665–676. [PubMed: 21375359]

- Mrena S, Kivelä T, Kurtio P, Auvinen A. Lens opacities among physicians occupationally exposed to ionizing radiation—a pilot study in Finland. *Scand J Work Environ Health*. 2011; 37:237–243. [PubMed: 21340441]
- Muirhead CR, O'Hagan JA, Haylock RGE, Phillipson MA, Willcock T, Berridge GLC, Zhang W. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. *Br J Cancer*. 2009; 100:206–212. [PubMed: 19127272]
- Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, Donaldson SS, Green DM, Sklar CA, Robison LL, Leisenring WM. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ*. 2009; 339:b4606. [PubMed: 19996459]
- Nakashima E, Carter RL, Neriishi K, Tanaka S, Funamoto S. Height reduction among prenatally exposed atomic-bomb survivors: a longitudinal study of growth. *Health Phys*. 1995; 68:766–772. [PubMed: 7759254]
- Nakashima E, Neriishi K, Minamoto A. A reanalysis of atomic-bomb cataract data, 2000–2002: a threshold analysis. *Health Phys*. 2006; 90:154–160. [PubMed: 16404173]
- Neriishi K, Nakashima E, Akahoshi M, Hida A, Grant EJ, Masunari N, Funamoto S, Minamoto A, Fujiwara S, Shore RE. Radiation dose and cataract surgery incidence in atomic bomb survivors, 1986–2005. *Radiology*. 2012; 265:167–174. [PubMed: 22875798]
- Otake M, Schull WJ. Radiation-related small head sizes among prenatally exposed A-bomb survivors. *Int J Radiat Biol*. 1993; 63:255–270. [PubMed: 8094424]
- Otake M, Schull WJ. Radiation-related brain damage and growth retardation among the prenatally exposed atomic bomb survivors. *Int J Radiat Biol*. 1998; 74:159–171. [PubMed: 9712546]
- Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, Sakata R, Sugiyama H, Kodama K. Studies of the mortality of atomic bomb survivors, report 14, 1950–2003: an overview of cancer and noncancer diseases. *Radiat Res*. 2012; 177:229–243. [PubMed: 22171960]
- Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K. Solid cancer incidence in atomic bomb survivors: 1958–1998. *Radiat Res*. 2007; 168:1–64. [PubMed: 17722996]
- Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950–1997. *Radiat Res*. 2003; 160:381–407. [PubMed: 12968934]
- Rafnsson V, Olafsdottir E, Hrafnkelsson J, Sasaki H, Arnarsson A, Jonasson F. Cosmic radiation increases the risk of nuclear cataract in airline pilots: a population-based case-control study. *Arch Ophthalmol*. 2005; 123:1102–1105. [PubMed: 16087845]
- Rastegar N, Eckart P, Mertz M. Radiation-induced cataract in astronauts and cosmonauts. *Graefes Arch Clin Exp Ophthalmol*. 2002; 240:543–547. [PubMed: 12136284]
- Richardson DB, Wing S. Radiation and mortality of workers at Oak Ridge National Laboratory: positive associations for doses received at older ages. *Environ Health Perspect*. 1999; 107:649–656. [PubMed: 10417363]
- Ridker PM. Inflammation, infection, and cardiovascular risk: how good is the clinical evidence? *Circulation*. 1998; 97:1671–1674. [PubMed: 9591759]
- Ross L, Johansen C, Dalton SO, Mellemkjær L, Thomassen LH, Mortensen PB, Olsen JH. Psychiatric hospitalizations among survivors of cancer in childhood or adolescence. *N Engl J Med*. 2003; 349:650–657. [PubMed: 12917301]
- Sadetzki S, Chetrit A, Mandelzweig L, Nahon D, Freedman L, Susser E, Gross R. Childhood exposure to ionizing radiation to the head and risk of schizophrenia. *Radiat Res*. 2011; 176:670–677. [PubMed: 22026716]
- Schervish, MJ. *Theory of statistics*. New York: Springer Verlag; 1995. p. 1-724.
- Schöllnberger H, Kaiser JC, Jacob P, Walsh L. Dose-responses from multi-model inference for the non-cancer disease mortality of atomic bomb survivors. *Radiat Environ Biophys*. 2012; 51:165–178. [PubMed: 22437350]
- Schöllnberger H, Kaiser JC, Walsh L, Jacob P. Reply to Little *et al.*: dose-responses from multi-model inference for the non-cancer disease mortality of atomic bomb survivors. *Radiat Environ Biophys*. 2013; 52:161–163. [PubMed: 23315228]

- Schull WJ, Otake M. Cognitive function and prenatal exposure to ionizing radiation. *Teratology*. 1999; 59:222–226. [PubMed: 10331523]
- Schultz-Hector S, Trott K-R. Radiation-induced cardiovascular diseases: is the epidemiologic evidence compatible with the radiobiologic data? *Int J Radiat Oncol Biol Phys*. 2007; 67:10–18. [PubMed: 17189062]
- Shimizu Y, Kodama K, Nishi N, Kasagi F, Suyama A, Soda M, Grant EJ, Sugiyama H, Sakata R, Moriwaki H, Hayashi M, Konda M, Shore RE. Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950–2003. *BMJ*. 2010; 340:b5349. [PubMed: 20075151]
- Skilton MR, Gosby AK, Wu BJ, Ho LML, Stocker R, Catterson ID, Celermajor DS. Maternal undernutrition reduces aortic wall thickness and elastin content in offspring rats without altering endothelial function. *Clin Sci (Lond)*. 2006; 111:281–287. [PubMed: 16734588]
- Stewart AM, Kneale GW. Non-cancer effects of exposure to A-bomb radiation. *J Epidemiol Community Health*. 1984; 38:108–112. [PubMed: 6747507]
- Stewart AM, Kneale GW. A-bomb survivors: factors that may lead to a re-assessment of the radiation hazard. *Int J Epidemiol*. 2000; 29:708–714. [PubMed: 10922349]
- Syndikus I, Tait D, Ashley S, Jannoun L. Long-term follow-up of young children with brain tumors after irradiation. *Int J Radiat Oncol Biol Phys*. 1994; 30:781–787. [PubMed: 7960979]
- Talbott EO, Youk AO, McHugh-Pemu KP, Zborowski JV. Long-term follow-up of the residents of the Three Mile Island accident area: 1979–1998. *Environ Health Perspect*. 2003; 111:341–348. [PubMed: 12611664]
- Tatsukawa Y, Nakashima E, Yamada M, Funamoto S, Hida A, Akahoshi M, Sakata R, Ross NP, Kasagi F, Fujiwara S, Shore RE. Cardiovascular disease risk among atomic bomb survivors exposed *in utero*, 1978–2003. *Radiat Res*. 2008; 170:269–274. [PubMed: 18763869]
- Travis LB, Hauptmann M, Gaul LK, Storm HH, Goldman MB, Nyberg U, Berger E, Janower ML, Hall P, Monson RR, Holm L-E, Land CE, Schottenfeld D, Boice JD Jr, Andersson M. Site-specific cancer incidence and mortality after cerebral angiography with radioactive thorotrast. *Radiat Res*. 2003; 160:691–706. [PubMed: 14640794]
- Tüchsen F, Hannerz H, Burr H. A 12 year prospective study of circulatory disease among Danish shift workers. *Occupational and Environmental Medicine*. 2006; 63:451–455. [PubMed: 16735480]
- Tukenova M, Guibout C, Oberlin O, Doyon F, Mousannif A, Haddy N, Guérin S, Pacquement H, Aouba A, Hawkins M, Winter D, Bourhis J, Lefkopoulos D, Diallo I, de Vathaire F. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. *J Clin Oncol*. 2010; 28:1308–1315. [PubMed: 20142603]
- United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Annex A. Epidemiological Studies of Radiation and Cancer. New York: United Nations; 2008a. UNSCEAR 2006 Report; p. 13-322.
- United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Annex B. Epidemiological Evaluation of Cardiovascular Disease and other Non-Cancer Diseases following Radiation Exposure. New York: United Nations; 2008b. UNSCEAR 2006 Report; p. 325-383.
- van Heyningen R. What happens to the human lens in cataract. *Sci Am*. 1975; 233:70–81. [PubMed: 1198089]
- von Sallmann L. The lens epithelium in the pathogenesis of cataract. *Trans Am Acad Ophthalmol Otolaryngol*. 1957; 61:7–19. [PubMed: 13409416]
- von Sallmann L, Grimes P, McElvain N. Aspects of mitotic activity in relation to cell proliferation in the lens epithelium. *Exp Eye Res*. 1962; 1:449–456. [PubMed: 13997872]
- Vrijheid M, Cardis E, Ashmore P, Auvinen A, Bae J-M, Engels H, Gilbert E, Gulis G, Habib RR, Howe G, Kurtinaitis J, Malke H, Muirhead CR, Richardson DB, Rodriguez-Artalejo F, Rogel A, Schubauer-Berigan M, Tardy H, Telle-Lamberton M, Usel M, Veress K. Mortality from diseases other than cancer following low doses of ionizing radiation: results from the 15-Country Study of nuclear industry workers. *Int J Epidemiol*. 2007; 36:1126–1135. [PubMed: 17666424]
- Wang C, Parmigiani G, Dominici F. Bayesian effect estimation accounting for adjustment uncertainty. *Biometrics*. 2012; 68:661–671. [PubMed: 22364439]

- Whincup P, Danesh J, Walker M, Lennon L, Thomson A, Appleby P, Hawkey C, Atherton J. Prospective study of potentially virulent strains of *Helicobacter pylori* and coronary heart disease in middle-aged men. *Circulation*. 2000; 101:1647–1652. [PubMed: 10758045]
- Wilde G, Sjöstrand J. A clinical study of radiation cataract formation in adult life following γ irradiation of the lens in early childhood. *Br J Ophthalmol*. 1997; 81:261–266. [PubMed: 9215051]
- Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998; 97:1837–1847. [PubMed: 9603539]
- Worgul BV, Kundiye YI, Sergiyenko NM, Chumak VV, Vitte PM, Medvedovsky C, Bakhanova EV, Junk AK, Kyrychenko OY, Musijachenko NV, Shylo SA, Vitte OP, Xu S, Xue X, Shore RE. Cataracts among Chernobyl clean-up workers: implications regarding permissible eye exposures. *Radiat Res*. 2007; 167:233–243. [PubMed: 17390731]
- Worgul BV, Merriam GR Jr, Medvedovsky C. Cortical cataract development—an expression of primary damage to the lens epithelium. *Lens Eye Toxic Res*. 1989; 6:559–571. [PubMed: 2487271]
- Yamada M, Naito K, Kasagi F, Masunari N, Suzuki G. Prevalence of atherosclerosis in relation to atomic bomb radiation exposure: an RERF Adult Health Study. *Int J Radiat Biol*. 2005; 81:821–826. [PubMed: 16484151]
- Yamada M, Wong FL, Fujiwara S, Akahoshi M, Suzuki G. Noncancer disease incidence in atomic bomb survivors, 1958–1998. *Radiat Res*. 2004; 161:622–632. [PubMed: 15161358]
- Zoric L, Miric D, Novakovic T, Pavlovic A, Videnovic G, Trajkovic G. Age-related cataract and serum albumin concentration. *Curr Eye Res*. 2008; 33:587–590. [PubMed: 18600491]

Table 1

Main types of circulatory disease. The circulatory diseases subtypes that are considered to be affected by radiation exposure appear in bold text.

<p>Congenital heart disease. Includes a range of abnormalities in heart structure or function that are present at birth. Such conditions could potentially be caused by irradiation of the foetus but obstetric irradiation is carefully controlled.</p> <p>Cardiac valve diseases. Include a variety of abnormalities to the heart valves including mitral stenosis and tricuspid regurgitation.</p> <p>Hypertrophic cardiomyopathy. Increased muscle density in the heart leading to less effective pumping of the blood.</p> <p>Cardiac Arrhythmias. Abnormally slow (bradycardia) or fast (tachycardia) beating of the heart often attributable to abnormalities in the electrical signalling that co-ordinates the beating of the four chambers of the heart.</p> <p>Pericarditis. Inflammation of the pericardium, the membrane that surrounds the heart, most frequently attributable to infectious agents but also well established to be caused by high doses of radiation.</p> <p>Coronary heart disease/congestive heart disease. Obstruction of the blood flow in the heart due to narrowing of cardiac vessels restricting blood and oxygen supply to the heart. In a mild form this leads to angina where the reduced blood flow leads to discomfort. When blockage is severe myocardial infarction (heart attack) occurs leading to acute heart failure.</p> <p>Stroke. Interruption of the blood supply to the brain due to blockage or rupture of vessels. Loss of blood and oxygen to areas can lead to cell death and consequently permanent brain dysfunction. Two majors forms of stroke are recognized, ischemic stroke caused by blockage due to blood clots forming locally (thrombotic stroke) or fragments from distant clots lodging in the brain vasculature (embolic stroke).</p>

Estimated Excess Relative Risks of Circulatory Disease in various Moderate and Low Dose Studies. (Adapted from Little *et al.* 2008; Little *et al.* 2010)). All data are in relation to underlying cause of death, unless otherwise indicated; CI: Confidence Interval; ICD: International Classification of Diseases

Table 2

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 <i>et al.</i> (2010)	0.1 (0–4) ^a	86,611 (n.a.)	Ischemic heart disease (ICD9 410–414)	0.02 (–0.10, 0.15)
				Myocardial infarction (ICD9 410)	0.00 (–0.15, 0.18)
				Hypertensive heart disease (ICD9 402, 404)	0.37 (0.08, 0.72)
				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)
				Hypertensive disease without heart disease (ICD9 401, 403, 405)	0.07 (–0.22, 0.55)
				Heart disease total (ICD9 393–429 excluding 401, 403, 405)	0.18 (0.11, 0.25) ^b
				Cerebral infarction (ICD9 433, 434)	0.04 (–0.10, 0.20)
				Cerebral hemorrhage (ICD9 431)	0.05 (–0.06, 0.17)
				Subarachnoid hemorrhage (ICD9 430)	0.30 (–0.04, 0.76)
				Other or unspecified cerebrovascular disease	0.16 (0.01, 0.34)
				Cerebrovascular disease total (ICD9 430–438)	0.12 (0.05, 0.19) ^b
				Circulatory disease apart from heart disease and stroke (ICD9 390–392, 401, 403, 405, 439–459)	0.58 (0.45, 0.72) ^b
				Other circulatory disease (ICD9 399–400, 406–409, 439–459)	–0.01 (<–0.01, 0.34)
Morbidity	Yamada <i>et al.</i> (2004)	0.1 (0–4) ^b	10,339 (n.a.)	All circulatory disease (ICD9 390–459)	0.15 (0.10, 0.20) ^b
				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

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)
Morbidity <i>in utero</i>	Tatsukawa <i>et al.</i> (2008)	0.001 (0–1.79)	506 (9,265)	Myocardial infarction incidence, 1964–1998 (ICD9 410)	0.12 (–0.16, 0.60) ^c
				Occlusion incidence, 1958–1998 (ICD9 433, 434)	0.06 (–0.11, 0.30) ^c
				Aortic aneurysm incidence, 1958–1998 (ICD9 441, 442)	0.02 (–0.22, 0.41) ^c
				Stroke incidence, 1958–1998 (ICD9 430, 431, 433, 434, 436)	0.07 (–0.08, 0.24) ^c
				Hypertension	0.20 (–0.39, 1.38)
Morbidity in childhood	Tatsukawa <i>et al.</i> (2008)	0.13 (0–3.53)	1,053 (20,216)	Nonfatal stroke or myocardial infarction	–0.91 (–1.00, 79.3)
				Hypertension	0.15 (–0.01, 0.34)
				Nonfatal stroke or myocardial infarction	0.72 (0.24, 1.40)
Occupational studies					
Mayak workers	Azizova <i>et al.</i> (2010a; 2010b)	0.83 (0–5.92) ^d	12,210 (248,030)	Acute myocardial infarction morbidity (ICD9 410)	0.015 (–0.090, 0.120) ^{d, e}
				Acute myocardial infarction mortality (ICD9 410)	0.258 (–0.005, 0.522) ^{d, e}
				Ischemic heart disease morbidity (ICD9 410–414)	0.119 (0.051, 0.186) ^{d, e}
				Ischemic heart disease mortality (ICD9 410–414)	0.066 (–0.018, 0.149) ^{d, e}
				Stroke morbidity (ICD9 430–432, 434, 436)	0.019 (–0.088, 0.127) ^{d, e}
				Stroke mortality (ICD9 430–432, 434, 436)	0.019 (–0.128, 0.166) ^{d, e}
				Cerebrovascular disease morbidity (ICD9 430–438)	0.449 (0.338, 0.559) ^{d, e}
				Cerebrovascular disease mortality (ICD9 430–438)	–0.018 (–0.115, 0.079) ^{d, e}
				Hypertension (ICD10 I10–I15) morbidity	0.26 (–0.04, 0.56)
				Essential hypertension (ICD10 I10) morbidity	0.36 (0.005, 0.71)
Chernobyl emergency workers	Ivanov <i>et al.</i> (2006)	0.109 (0–>0.5)	61,017 (n.a.)	Hypertensive heart disease (ICD10 I11) morbidity	0.04 (–0.36, 0.44)
				Ischemic heart disease (ICD10 I20–I25) morbidity	0.41 (0.05, 0.78)
				Acute myocardial infarction (ICD10 I21) morbidity	0.19 (–0.99, 1.37)
				Other acute ischemic heart disease (ICD10 I24) morbidity	0.82 (–0.62, 2.26)
				Angina pectoris (ICD10 I20) morbidity	0.26 (–0.19, 0.71)
				Chronic ischemic heart disease (ICD10 I25) morbidity	0.20 (–0.23, 0.63)

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)
German uranium miner study	Kreuzer <i>et al.</i> (2013)	0.041 (0–0.909) ^d	58,982 (2,180,639)	Other heart disease (ICD10 I30–I52) morbidity	–0.26 (–0.81, 0.28)
				Cerebrovascular disease (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)
EdF workers	Laurent <i>et al.</i> (2010)	0.0215 (0–0.6)	22,393 (440,984)	All circulatory disease (ICD10 I00–I99) morbidity	0.18 (–0.03, 0.39)
				All circulatory disease (ICD10 I00–I99)	–0.13 (–0.38, 0.12) ^d
				Ischaemic heart disease (ICD10 I20–I25)	–0.03 (–0.38, 0.32) ^d
				Cerebrovascular disease (ICD10 I60–I69)	0.44 (–0.16, 1.04) ^d
Eldorado uranium miners and processing (male) workers	Lane <i>et al.</i> (2010)	0.0522 (<0.0234 – >0.1215)	16,236 (508,673)	Ischaemic heart disease	4.1 (–2.9, 13.7) ^f
				Cerebrovascular disease	17.4 (0.2, 43.9) ^f
				All circulatory disease	2.7 (–2.3, 9.1) ^f
				Ischemic heart disease	0.15 (–0.14, 0.58)
BNFL workers	McGeoghegan <i>et al.</i> (2008)	0.0569 (0 – >0.729)	38,779 (1,081,570)	Stroke	–0.29 (<–0.29, 0.27)
				All other circulatory disease	0.07 (<–0.33, 0.77)
				Ischemic heart disease (ICD9 410–414)	0.70 (0.37, 1.07) ^{b,f}
				Cerebrovascular disease (ICD9 430–438)	0.66 (0.17, 1.27) ^{b,f}
3 rd Analysis of UK National Registry for Radiation Workers	Muirhead <i>et al.</i> (2009)	0.0249 (<0.01 – >0.4)	174,541 (3.9 × 10 ⁶)	Other circulatory diseases (ICD9 390–398, 415–429, 440–459)	0.83 (–0.10, 1.12) ^f
				Circulatory diseases apart from cerebrovascular (ICD9 390–429, 439–459)	0.72 (0.39, 1.10) ^f
				All circulatory disease (ICD9 390–459)	0.54 (0.30, 0.82) ^{b,f}
				All circulatory disease (ICD9 390–459)	0.251 (–0.01, 0.54)
				Circulatory disease not strongly related to smoking (ICD9 390–409, 415–440, 442–459)	0.280 (–0.19, 0.85)
				Aortic aneurysm (ICD9 441)	–0.132 (–1.29, 1.92)
				Ischemic heart disease (ICD9 410–414)	0.259 (–0.05, 0.61)

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)
US Oak Ridge workers	Richardson and Wing (1999)	n.a. (0 – >0.1)	14,095 (425,486)	Cerebrovascular disease (ICD9 430–438)	0.161 (–0.42, 0.91)
				Ischemic heart disease (ICD8 410–414)	–2.86 (–6.90, 1.18)
IARC 15-country nuclear worker study	Vrijheid <i>et al.</i> (2007)	0.0207 (0.0 – >0.5)	275,312 (4,067,861)	Circulatory disease (ICD10 I00–I99, J60–J69, O88.2, R00–R02, R57)	0.09 (–0.43, 0.70)
				Ischemic heart disease (ICD10 I20–I25)	–0.01 (–0.59, 0.69)
				Heart failure (ICD10 I50)	–0.03 (<0, 4.91)
				Deep vein thrombosis and pulmonary embolism (ICD10 I26, I80, I82, O88.2)	–0.95 (–1.00, 9.09) ^g
				Cerebrovascular disease (ICD10 I60–I69)	0.88 (–0.67, 3.16)
				All other circulatory disease (ICD10 R00–R02, R57, I00–I99 excluding I20–26, I50, I60–69, I80, I82)	0.29 (<0, 2.40)
Environmental studies					
Three Mile Island study	Talbott <i>et al.</i> (2003)	0.0001 (0 – >0.00016)	32,135 (561,063)	Heart disease (white males)	–274 (–874, 438)
Techa River study	Krestinina <i>et al.</i> (2013)	0.035 (0–0.51) ^h	29,735 (901,563)	Heart disease (white females)	–951 (–1433, –390)
				All circulatory disease mortality (ICD9 390–459) (10 year lag)	0.24 (–0.08, 0.59)
				All circulatory disease mortality (ICD9 390–459) (15 year lag)	0.36 (0.02, 0.75)
				Ischaemic heart disease mortality (ICD9 410–414) (10 year lag)	0.40 (–0.11, 0.99)
				Ischaemic heart disease mortality (ICD9 410–414) (15 year lag)	0.56 (0.01, 1.19)
Semipalatinsk nuclear test study	Grosche <i>et al.</i> (2011)	0.09 (0–0.63) ^d	19,545 (582,656)	Heart disease (ICD9 410–429): all settlements	3.22 (2.33, 4.10) ^d
				Heart disease (ICD9 410–429): exposed settlements	0.06 (–0.39, 0.52) ^d
				Stroke (ICD9 430–438): all settlements	2.96 (1.77, 4.14) ^d
				Stroke (ICD9 430–438): exposed settlements	–0.06 (–0.65, 0.54) ^d
				Cardiovascular disease (ICD9 390–459): all settlements	3.15 (2.48, 3.81) ^d
				Cardiovascular disease (ICD9 390–459): exposed settlements	0.02 (–0.32, 0.37) ^d

^a analysis based on colon dose.

Little

Page 23

- b* analysis using underlying or contributing cause of death.
- c* analysis based on stomach dose, derived from Table 4 of Yamada *et al.* (2004) with smoking and drinking in the stratification.
- d* risk estimates in relation to cumulative whole body external gamma dose.
- e* assuming a lag period of 10 years.
- f* 90% CI.
- g* estimate derived from log-linear model, evaluated at 1 Sv.
- h* analysis based on dose to muscle.

Table 3

Threshold dose estimates for cataract (with 95% CI). LOCS: Lens Opacities Classification System; CI: Confidence Interval; ERR: excess relative risk; EAR: excess absolute risk; AHS: Adult Health Study

Cohort	Ascertainment	Endpoint	Threshold dose estimate (Gy)
A-bomb AHS examination (Nakashima <i>et al.</i> 2006)	LOCS II	Cortical	0.6 (<0, 1.2) ^{a b}
		Posterior subcapsular	0.7 (<0, 2.8) ^{a b}
A-bomb AHS cataract surgery (Neriishi <i>et al.</i> 2012)	Surgical removal	All cataract, ERR model	0.50 (0.10, 0.95)
		All cataract, EAR model	0.45 (0.10, 1.05)
Chernobyl recovery worker (Worgul <i>et al.</i> 2007)	Merriam-Focht	Non-nuclear stage 1	0.50 (0.17, 0.69)
		Superficial cortical stage 1	0.34 (0.18, 0.51)
		Posterior subcapsular stage 1	0.35 (0.19, 0.66)
		Stage 1 cataract	0.34 (0.19, 0.68)
		All cataract stage 1–5	0.50 (0.17, 0.65)

^a 90% CI

^b Sv.

Table 4

Cataract risk estimates. Excess odds ratio (/Gy) (+95% CI). LOCS: Lens Opacities Classification System; EOR: excess odds ratio; AHS: Adult Health Study; WHO: World Health Organization; CI: confidence interval

Cohort	Ascertainment	Endpoint	Excess odds ratio (EOR) Gy ⁻¹ (95% CI)
Swedish skin haemangioma (Hall <i>et al.</i> 1999)	LOCS I	Cortical	0.50 (0.15, 0.95)
		Posterior subcapsular	0.49 (0.07, 1.08)
A-bomb AHS (Nakashima <i>et al.</i> 2006)	LOCS II	Cortical	0.30 (0.10, 0.53) ^a
		Posterior subcapsular	0.44 (0.19, 0.73) ^a
		Nuclear opacity	0.07 (−0.11, 0.30) ^a
		Nuclear colour	0.01 (−0.17, 0.24) ^a
A-bomb AHS cataract surgery (Neriishi <i>et al.</i> 2012)	Surgical removal	All cataract removal	0.32 (0.17, 0.52) ^b
Icelandic airline pilots (Rafnsson <i>et al.</i> 2005)	WHO	Nuclear	20 (0, 30)
		Cortical	<0 (<0, >0)
		Posterior subcapsular	<0 (<0, >0)
Chernobyl recovery workers (Worgul <i>et al.</i> 2007)	Merriam-Focht	Non-nuclear stage 1–5	0.65 (0.18, 1.30)
		Posterior subcapsular stage 1	0.42 (0.01, 1.00)
		Nuclear	0.07 (−0.44, 1.04)
		All cataract stage 1–5	0.70 (0.22, 1.38)
US Radiologic technologist (Chodick <i>et al.</i> 2008)	Self-reported removal	All cataract removal	2.0 (−0.7, 4.7)
Finnish interventional radiologists (Mrena <i>et al.</i> 2011)	LOCS II	Cortical or posterior excluding nuclear	4 (−20, 28)
		All opacity	13 (−2, 28)

^aEOR Sv^{−1}.

^badjusted to persons in Hiroshima, aged 70, exposed at age 20 years.