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Occupational radiation exposure and risk of cataract incidence in a cohort of US radiologic technologists

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Abstract

It has long been known that relatively high-dose ionising radiation exposure (>1 Gy) can induce cataract, but there has been no evidence that this occurs at low doses (<100 mGy). To assess low-dose risk, participants from the US Radiologic Technologists Study, a large, prospective cohort, were followed from date of mailed questionnaire survey completed during 1994-1998 to the earliest of self-reported diagnosis of cataract/ataract surgery, cancer other than non-melanoma skin, or date of last survey (up to end 2014). Cox proportional hazards models with age as timescale were used, adjusted for *a priori* selected cataract risk factors (diabetes, body mass index, smoking history, race, sex, birth year, cumulative UVB radiant exposure). 12,336 out of 67,246 eligible technologists reported a history of diagnosis of cataract during 832,479 person years of follow-up, and 5509 from 67,709 eligible technologists reported undergoing cataract surgery with 888,420 person years of follow-up. The mean cumulative estimated 5-year lagged eye-lens absorbed dose from occupational radiation exposures was 55.7 mGy (interquartile range 23.6-69.0 mGy). Five-year lagged occupational radiation exposure was strongly associated with self-reported cataract, with an excess hazard ratio/mGy of 0.69×10^{-3} (95% CI 0.27×10^{-3} to 1.16×10^{-3} , $p < 0.001$). Cataract risk remained statistically significant ($p = 0.030$) when analysis was restricted to <100 mGy cumulative occupational radiation exposure to the eye lens. A

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non-significantly increased excess hazard ratio/mGy of 0.34×10^{-3} (95% CI -0.19×10^{-3} to 0.97×10^{-3} , $p=0.221$) was observed for cataract surgery. Our results suggest that there is excess risk for cataract associated with radiation exposure from low-dose and low dose-rate occupational exposures.

Keywords

ionising radiation; cataract; cataract surgery; threshold; tissue reaction effects; diabetes; low dose rate; questionnaire-based assessment

Introduction

By age 75 years over half of the US population will have a cataract (<https://www.nei.nih.gov/eyedata/ataract>). Well over a million cataract surgeries are performed per year in the US, at the cost of several billion dollars per year (1). Well-established risk factors for cataracts include solar radiation, and specifically solar ultraviolet radiation (UVR) exposure (2), diabetes, high body mass index (BMI), cigarette smoking, use of corticosteroid medicine and ocular trauma (3-6).

It has long been known that relatively high radiation doses of 1 Gy or more can induce cataract (7). It has conventionally been assumed that cataract is a tissue-reaction (formerly deterministic) effect, so that no excess risk would be expected below a threshold dose of about 500 mGy (7, 8). Accumulating evidence from follow-up studies of the Japanese atomic bomb survivors (9-11), Chernobyl clean-up workers (12), US astronauts (13, 14) and other populations (15-17) suggests that cataracts may be induced by somewhat lower doses, of the order of 100-250 mGy (12), of ionising radiation, but none of these studies have suggested risks below 100 mGy, the level conventionally used to define low dose (18). Only in the study of atomic bomb survivors was there any test for modification of radiation risk by lifestyle and medical covariates, specifically diabetes, sex, age at exposure and time since exposure (10). Our previous study of the US radiologic technologists (USRT) cohort, based on follow-up through 2005 and using an earlier dosimetry system to approximate eye-lens radiation absorbed doses, found 2382 incident cataracts and 647 cataract extractions, and suggested, albeit weakly, that relatively low levels of cumulative radiation exposure, on the order of 60 mGy, were associated with risk of cataract and cataract surgery (19). More recently we found an excess risk of cataract among the subgroup of the USRT cohort working with nuclear medicine procedures based on work history information (20).

In this report, we evaluate risks associated with self-reported questionnaire-derived history of cataracts and cataract surgery in the USRT cohort in relation to estimated cumulative absorbed dose from occupational radiation exposures. Our assessment used an updated and improved eye-lens dosimetry (21) and an additional nine years of follow-up from the previous analysis (19), yielding at least a five-fold increase in the number of self-reported cataracts and cataract surgeries. Our study included data collected on a broad range of known and suspected risk factors for cataract. The statistical power to assess low-dose effects and possible lifestyle and medical modifying factors is therefore substantially increased.

Data and Methods

Study population and follow-up

Overview of USRT study—The USRT study population, cohort follow-up, and dosimetry methods have been described elsewhere (21-23) (see also www.radtechstudy.nci.nih.gov). Briefly, the US National Cancer Institute, in collaboration with the University of Minnesota and the American Registry of Radiologic Technologists (ARRT), is studying cancer and other serious health effects in relation to low-to-moderate dose protracted ionising radiation among 146,021 (106,952 women) US radiologic technologists who were certified for at least two years during 1926-1982 (24, 25). Active follow-up was conducted through yearly re-certification with the ARRT. Inactive registrants were linked with national and other databases, including the Social Security Administration and National Death Index, to determine vital status and obtain causes of death. Four questionnaires were administered during 1983–1989, 1994–1998, 2003–2005, and 2012-2014 to collect information on health outcomes (including self-reports of cataract and cataract surgery in all but the first questionnaire), work history, demographic and lifestyle characteristics, and medical histories. The first and second questionnaires were sent to all eligible participants, while the third and fourth questionnaires were sent only to cohort members who had responded to the first and/or the second questionnaire. The response rate for each of the questionnaires among living and located cohort members was 68-72% for the first three surveys and 63% for the fourth survey, with 110,373 individuals completing one or more questionnaires.

Eligible study population and follow-up—Since data on cataract and cataract surgery were only elicited in the second through fourth questionnaires, we only included responders to the second or third questionnaire and at least one subsequent questionnaire for follow-up of these ocular endpoints. We censored follow-up after a diagnosis of cancer (other than non-melanoma skin cancer [NMSC]) because of the potential for radiotherapy that the subject might receive. After excluding 8252 technologists who reported a history of radiotherapy on the first or second surveys, and (a) a further 1217 with inconsistent questionnaire responses for cataract and 33,658 who were not informative for cataract (because they had cataract at first questionnaire responded to, or gave incomplete information in subsequent questionnaires), or (b) 343 with inconsistent responses for cataract surgery and a further 32,532 not informative for this endpoint (for analogous reasons as those for cataract morbidity), and excluding also 1536 persons reporting cataract at the first questionnaire responded to, there were a total of 67,246 technologists eligible for study of cataract and 67,709 eligible for study of cataract surgery (see Appendix A Figure A1 for a flow diagram showing the exclusions). Further details on eligibility criteria are given in Appendix A. As implied by Appendix A, cataract surgeries are not a subset of cataract cases, nor vice versa.

Individuals were deemed at risk for developing cataract or undergoing cataract surgery during any of the time periods between completion of the (a) second to third questionnaire, (b) second to fourth questionnaire, and (c) third to fourth questionnaire. For each endpoint, namely (1) self-reported history of diagnosis of cataract (henceforth termed “cataract

history”), and (2) self-reported cataract surgery (henceforth termed “cataract surgery”), individuals were included in each inter-questionnaire period during which they were free of these outcomes (i.e., did not report either (1) a history of diagnosis of cataract, or (2) undergoing cataract surgery, respectively at the first of the pair of questionnaires), and had unambiguous indication of cataract history and year of diagnosis, or of cataract surgery and year of surgery, respectively, at the second of the pair of questionnaires. Follow-up terminated at the earliest of (a) date of first cataract history, or date of first cataract surgery, respectively, (b) date the final questionnaire was completed, or (c) the date of diagnosis of any cancer other than NMSC. Further details on the precise definitions of dates of start and end of follow-up per individual are given in Appendix A.

Dosimetry

Occupational doses—A historical dose reconstruction was undertaken to estimate annual radiation absorbed doses to specific organs from occupational exposure for each radiologic technologist, described in more detail in Appendix B and in Simon *et al.* (21). Annual reported badge doses were used for each technologist when available; otherwise, doses were estimated from probability density functions based on population exposure data for each year worked, modified by a work history questionnaire-derived exposure score. All annual reported badge doses, in terms of personal dose equivalent ($H_p(10)$) (mSv), were estimated up to December 31st 1997. The individual annual dose estimates used in analyses were regression-calibration estimates, adjusted for dose uncertainties (26). Questionnaire response was used to modify badge doses for the estimation of eye-lens absorbed doses. The doses reflect exposures from performing or assisting in diagnostic and therapeutic radiological procedures, and were mostly from x-rays (21). Most radiologic technologists performed or assisted with multiple procedures, including standard fluoroscopy and multi-film and routine diagnostic radiography. A substantial fraction also worked with fluoroscopically-guided interventional procedures, and a smaller percentage with radio-pharmaceutical procedures (21, 27). Eye-lens absorbed doses were estimated from measured or estimated personnel monitoring badge doses using badge-dose-to-organ-absorbed-dose conversion factors based on beam energy (kV) and x-ray beam filtration specific to each kV and time period (28).

Covariates

The following questionnaire-derived variables were selected *a priori* as adjusting covariates in most regression models because of their known effect on cataract prevalence (3-5), and because they were considered potential confounders in the relationship with radiation dose. These variables included sex, racial/ethnic group, birth year, diabetes, BMI, smoking status (current smoker/ex-smoker/never smoker, numbers of cigarettes/day, age stopped smoking), and cumulative ambient UVB radiant exposure (Appendix C). Cataract is thought to result from cumulative oxidative stress in the eye lens (29), one component of which is associated with cumulative UVA exposure, as UVA is thought more directly capable of penetrating to the eye lens than UVB (30). However, as UVA and UVB are highly correlated (also correlated with total solar exposure)(see Appendix C) it suffices to use UVB for adjustment purposes. Corticosteroid use, a well known risk factor for cataract (4), was not elicited on any of the USRT questionnaires. Data for the *a priori*-specified potential confounding

variables were obtained from the first questionnaire responded to. Because UVB radiation can only be estimated for the subset of persons who answered the third questionnaire, an indicator for UVB missing data was also included in the baseline risk model.

Statistical methods

Risks for cataract and cataract surgery were assessed using Cox proportional hazards models (31), with age as the timescale, in which the hazard ratio (HR) (which is the same thing as the relative risk computed at a particular instant) for individual i at age a was given by:

$$HR_i[a, D_i, (X_{ji}) | \alpha, (\beta_j)] = \exp \left[\sum_{j=1}^N \beta_j X_{ji} \right] [1 + \alpha D_i(a - 5)] \quad (1)$$

where $D_i(a - 5)$ is the time-varying cumulative eye-lens absorbed dose in mGy, lagged by 5 years to allow for disease latency (8, 17), (X_{ji}) are the lifestyle (e.g., cigarette smoking history), environmental (e.g., UVB), and medical risk factors (e.g., diabetes, obesity), α is the excess HR coefficient (EHR) (which is same thing as the excess relative risk computed for a particular instant) per unit eye-lens dose (mGy), and (β_j) are coefficients adjusting for other risk factors. So it is in some sense the case that $EHR \times D = HR - 1$. A detailed description of the method used to estimate age at entry and exit are described in Appendix A. We also conducted analysis taking into account variation in cataract risk in relation to dose accumulated in various temporal windows, of time from the indicated radiation exposure to the time at risk and from age at exposure to the time at risk. Further details are given in Appendix D. Additional sensitivity analyses were conducted using lag periods of 0 to 10 years (Appendix D Table D1). Models were also fitted using linear-exponential forms of dose response (Appendix D Table D2).

As indicated above, persons with previous radiotherapy were selected *a priori* as a category that should be excluded, and for similar reasons persons developing cancer other than NMSC were censored at occurrence of cancer, because of the potential of such cancer to be treated with radiotherapy. Indeed, preliminary analysis performed suggested that both radiotherapy and cancer other than NMSC were correlated with the cataract or cataract surgery and with occupational radiation exposure, and as such were potential confounders (analysis not shown). Nevertheless, we also show analysis in which persons with radiotherapy were added back in or cancer censoring was removed (Appendix D Table D3).

For reasons outlined more precisely in Appendix D all model fits to cataract surgery were restricted to those without cataract incidence at baseline questionnaire, and employed adjustment to the baseline hazard for time since baseline questionnaire (an indicator variable for this quantity being <5 years) and restricted radiogenic excess risk to the period 5 years from baseline questionnaire.

The HRs given in Tables 1 and 2 were derived using model (1) without any additional adjustment. In Table 2, the dose used is the cumulative eye-lens absorbed dose from occupational exposures up to December 31, 1997, the final date for which absorbed dose

could be estimated based on badge dose data availability. In Tables 3, 4 and 5, eye-lens absorbed dose was treated as a time varying measure, and lagged by 5 years. Likewise, cumulative UVB radiant exposure was treated as time varying, and lagged by 5 years.

Except where indicated, analyses of all endpoints in Tables 3, 4 and 5 and Figure 1 were adjusted by stratification for year of birth (categorized by: <1900, 1900-1909, ..., 1950-1959, 1960), sex and race, and via adjustment to the baseline hazard for the *a priori*-determined risk factors for cataract, for the reasons given above. Nevertheless we provide (in Appendix D Table D4) analysis in which selected variables are removed as stratifying/adjusting variables. Wherever possible, these variables were derived from the first questionnaire responded to (of the second or third questionnaires). All analyses were carried out using R (32) and Epicure (33). More details are given in Appendix D.

Ethical approval

This study has been approved annually by the National Cancer Institute Special Studies Institution Review Board and by the University of Minnesota Institutional Review Board.

Data sharing

The data and all code used for the analysis are available from the lead author on application.

Contributors

MPL, CMK and MSL conceived and designed the study, and produced an analytical plan. MSL, MMD, BHA, MPL and JSM were responsible for acquisition and processing of data (including questionnaire, mortality, and cancer validation data). SLS, DLP, MMD, JSM, MSL, BHA, MPL and DB were responsible for dose estimation and validation. MPL was responsible for data analysis. MPL, CMK, MSL, DB, NH and CM interpreted the results. MPL produced a first draft of the manuscript. All authors reviewed the manuscript and provided intellectual input. MPL, CMK and MSL are guarantors.

Competing interests

All authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

Results

There were 12,336 cases of cataract history among 67,246 eligible subjects and 5509 cataract surgeries among 67,709 eligible subjects (Table 1). There were 832,479 and 888,420 person years of follow-up for the groups eligible for the cataract history and cataract surgery analyses, respectively, representing an average of 12.4 and 13.1 years of follow-up per person for cataract history and cataract surgery, respectively. Higher risks of cataract history and cataract surgery were observed among women compared to men, whites compared to blacks or other racial/ethnic groups, among those reporting in the baseline interview a diagnosis of diabetes compared to no diabetes, among those who were obese

(BMI ≥ 30 kg/m²) at baseline compared to those with normal weight, and among those who were current cigarette smokers compared to those who never smoked (heterogeneity $p < 0.001$ in all cases), with progressive increases in risks with increasing smoking quantity (cigarettes/day) and increasing age at stopping smoking (Table 1). There were significantly increased risks with increasing cumulative UVB radiant exposure (treated as a time-varying variable) for cataract history and for cataract surgery, with similar magnitude of increases in risk for both endpoints, with EHR / MJ cm⁻² = 3.52 (95% CI 0.57, 7.64) ($p = 0.016$) for cataract, = 4.86 (95% CI 0.41, 12.45) ($p = 0.028$) for cataract surgery (data not shown). The mean cumulative eye-lens absorbed dose among those eligible for study of cataract history was 55.7 mGy, with interquartile range 23.6–69.0 mGy; for those eligible for study of cataract surgery, the mean cumulative dose was 55.0 mGy, with interquartile range 23.8–68.9 mGy (data not shown).

Table 2 shows the unadjusted risk by cumulative eye-lens absorbed dose group for cataract history and cataract surgery. As can be seen, there was a progressive increase in HR with dose for cataract history, and (to a lesser extent) also for cataract surgery. Table 2 shows that there were 3072 cases of cataract history and 1571 of cataract surgery with cumulative occupational dose ≥ 100 mGy at baseline.

Table 3 indicates that there was a significant increase in risk of cataract history over the full dose range, with EHR/mGy = 0.69×10^{-3} (95% CI 0.27×10^{-3} , 1.16×10^{-3} , $p < 0.001$), which increases in magnitude with increasingly lower restriction of dose, so that when analysis was restricted to < 100 mGy the EHR/mGy = 1.16×10^{-3} (95% CI 0.11×10^{-3} , 2.31×10^{-3} , $p = 0.030$). The exposure-response trend for occupational radiation and increase in cataract surgery was positive, but non-significant over the full (EHR/mGy = 0.34×10^{-3} , 95% CI -0.19×10^{-3} , 0.97×10^{-3} , $p = 0.221$) and restricted dose ranges, although in contrast with cataract history, the trend did not change appreciably with increasingly lower restriction of dose (Table 3). Related to this, both cataract history and cataract surgery exhibited declining excess risks per unit dose with increasing dose, as shown in Figure 1, which was conventionally statistically significant ($p = 0.015$) for cataract history but not for cataract surgery ($p > 0.5$). The degree of reduction in EHR/mGy with increasing dose was generally comparable for the two outcomes. The evidence for change in the magnitude of EHR/mGy with increasing dose became much weaker in models that included modification of radiation risk by attained age ($p = 0.080$), and remained non-significant for cataract surgery ($p > 0.5$) (Appendix D Table D2).

Table 4 demonstrates that risk of cataract history among diabetics was appreciably lower, with an EHR/mGy of -0.95×10^{-3} (95% CI -1.57×10^{-3} , 0.03×10^{-3}), compared with non-diabetics, with an EHR/mGy of 0.85×10^{-3} (95% CI 0.40×10^{-3} , 1.34×10^{-3}), a difference which was highly statistically significant ($p = 0.002$). Similar differences were seen in radiation risk of cataract surgery among diabetics and non-diabetics. There were indications at borderline levels of statistical significance ($p = 0.083$) that radiation-related risk of cataract history decreased with increasing attained age. There was little evidence for modification of the cataract or cataract surgery radiation risk by sex, racial group, smoking (overall smoking status, number of cigarettes smoked, age stopped smoking), birth year, BMI or by cumulative UVB radiant exposure (Table 4).

Table 5 does not suggest that there was significant variation of radiation-related risk of cataract history by time since exposure ($p=0.323$) or age at exposure ($p=0.362$). Nevertheless, there was progressive reduction in the radiation risk of cataract history with increasing age at exposure; comparing those exposed <30 years old to those exposed at ages 30-49 and to those exposed at ages ≥ 50 , the EHR/mGy declined from 0.91×10^{-3} (95% CI 0.35×10^{-3} , 1.53×10^{-3}), 0.42×10^{-3} (95% CI -0.40×10^{-3} , 1.30×10^{-3}) and -0.47×10^{-3} (95% CI -3.20×10^{-3} , 2.86×10^{-3}), respectively. Likewise, there was some reduction in cataract risk with increasing time since exposure, so that for <10 years after exposure, 10-14 years after exposure and ≥ 15 years after exposure, the EHR/mGy were 8.71×10^{-3} (95% CI -1.77×10^{-3} , 20.34×10^{-3}), -0.91×10^{-3} (95% CI -6.81×10^{-3} , 5.74×10^{-3}) and 0.66×10^{-3} (95% CI 0.23×10^{-3} , 1.14×10^{-3}), respectively.

Little difference was made to the dose response risk estimate, or to the overall goodness of fit by varying the lagging period between 0 and 10 years (Appendix D Table D1). Nevertheless, there were weak indications, suggested by the minimising point of the $-\log$ -likelihood, that a dose lag of 4-5 years was optimal.

Adding back persons with prior radiotherapy recorded on the first two questionnaires, or not censoring individuals at occurrence of cancer other than NMSC, or both, had little effect on the risk of cataract history and cataract surgery risk estimates (Appendix D Table D3). Apart from sex and birth year, selective removal of variables used for stratifying or adjusting the baseline risk also made little difference on the cataract risk (Appendix D Table D4). Sensitivity analysis in which the restriction on absence of cataract at baseline questionnaire, or removing the restriction on the radiogenic excess starting ≥ 5 years after the baseline questionnaire made little difference to cataract surgery risk (Appendix D Table D5).

Discussion

The cohort of US radiologic technologists prospectively followed for an average of 12-13 years is the first study to identify a significant exposure response of cumulative occupational radiation exposures to the eye lens under 100 mGy and risk of cataracts based on self-reported history. The very large number of technologists with self-reported cataract (12,336) exceeds that in all other radiation-exposed cohorts by more than 3-fold. Based on another novel feature of the study, the availability of information on a broad-based list of known and probable cataract risk factors at baseline, we found that a history of diabetes significantly modified the radiation-cataract relationship, revealing a markedly lower risk of occupational radiation-associated cataracts among technologists with diabetes. We observed modest, albeit non-significant reductions in risk of cataract history with increasing time after exposure and age at occupational radiation exposure. We observed a non-significant exposure response association of cumulative occupational radiation dose with self-reported cataract surgery. The novelty of this occupational study is that, in contrast to many previous studies of cataract (see Table 6), the dose rates are typically low (<5 mGy/hour).

In general, the EHR estimates for cataract history given in Table 3 $0.69 \times 10^{-3} \text{ mGy}^{-1}$ (95% CI 0.27×10^{-3} , 1.16×10^{-3}), and for cataract surgery, $0.34 \times 10^{-3} \text{ mGy}^{-1}$ (95% CI -0.19×10^{-3} , 0.97×10^{-3}), are statistically consistent with those observed in other radiation-exposed

groups (see Table 6), in particular, the Japanese atomic bomb survivors (9-11) and the Chernobyl clean-up workers (12). The excess odds ratio (EOR) (which approximates our incidence-based EHR of $0.69 \times 10^{-3} \text{ mGy}^{-1}$ (95% CI 0.27×10^{-3} , 1.16×10^{-3})) in those two groups generally lie in the range $0.30\text{-}0.70 \times 10^{-3} \text{ mGy}^{-1}$. There is reasonably consistent evidence for excess risk of both posterior subcapsular cataract and cortical cataract incidence associated with radiation exposure. In general, nuclear cataract, which is the dominant type of cataract in adulthood, appears not to be radiation related (17).

In the previous cataract analysis of the USRT cohort, follow-up was considerably shorter (through 2005 *vs* through 2014 in the current study) and an earlier, less sophisticated version of the dosimetry system was used. In the earlier investigation, age at baseline questionnaire was restricted to 25-44 years, cataract occurrence was restricted to those under 50 years of age, and some high-dose technologists and those who never worked, were excluded, in contrast to the lack of such exclusions in the current study. An elevated risk of cataract that did not attain statistical significance (EHR = $2.0 \times 10^{-3} \text{ mGy}^{-1}$, 95% CI -0.7×10^{-3} , 4.7×10^{-3}) was observed in the earlier study (19) (Table 6). The dosimetry used in the earlier analysis was not validated in the same way as has been done for the dosimetry employed here (as discussed at greater length below), nor was there any attempt made to assess modifications of radiation risk by major lifestyle, medical and environmental risk factors. This together with the substantially smaller number of cataracts, by at least a factor of 5 compared with the present analysis ($n=2,382$ in the earlier investigation *vs* 12,366 in the current study) and by at least a factor of 14 for cataract surgery ($n=384$ in the earlier investigation *vs* 5509 in the current study), suggests that the current analysis and findings should supersede the earlier results.

The International Commission on Radiological Protection (ICRP) has classified cataract as a tissue reaction (or deterministic) effect (8), with a threshold dose of 500 mGy below which no excess risk would be expected. A linear-threshold model such as implicitly used for tissue-reaction effects by ICRP implies an upwardly curving dose response. The Japanese atomic bomb survivor data showed evidence of a significant (i.e., non-zero) threshold dose of about 500 mGy below which there would be no excess risk, implying some degree of upward curvature in the dose response; however, at distinct variance with this finding, there was no evidence of linear-quadratic curvature in the dose response in the atomic bomb survivors (10). There was also evidence of a significant threshold, at about 300-400 mGy, for various cataract endpoints in a cohort of Chernobyl clean-up workers (12). Again at variance with their findings, using a conventional linear-quadratic model, the authors found little evidence of upward curvature in the cataract dose response as would be expected if a linear-threshold model were valid (12). There are well known methodological problems with fitting of threshold models, discussed elsewhere (17), so that likelihood-based *p*-values and confidence intervals of the threshold value may be incorrect. The discrepancy between the results of fitting threshold and linear-quadratic models to the Japanese atomic bomb survivor and Chernobyl datasets (10, 12) strongly suggests that this is the case. Although we have not formally tested for a dose threshold given these methodological concerns, we did assess curvature in the dose response, and found some indication of reduction of excess risk with increasing dose (Figure 1). This became much weaker (and no longer statistically significant) when radiation risk was also modified by attained age. Based on our results, a

threshold of 500 mGy is inconsistent with the pattern of excess risk (Figure 1, Table 3) in the present cohort.

Our findings that EHR/Gy decreased with increasing time since exposure and age at exposure (albeit not statistically significant) in the current study (Table 5), are in agreement with what has been seen in the Japanese atomic bomb survivors (10) and in the Swedish haemangioma patients (34). The non-significantly larger risks for women than for men contrasts with the reverse direction of effect (at borderline levels of significance, $p=0.03$) seen in the atomic bomb survivors,(10) but the marginal significance suggests that not too much should be made of this difference. Diabetes, high BMI, and cigarette smoking are well established risk factors for cataract (4, 10, 12, 19), as also shown here (Table 1), although there was no suggestion that they confounded the radiation dose response in our study (Appendix D Table D4) or other studies in which these were evaluated(10, 12). However, diabetes does strongly modify radiation risk in the USRT, so that those with this condition have much reduced risk of cataract and cataract surgery in contrast with the Japanese atomic bomb survivors (10).

Strengths of the present study include the large population with low (mostly <100 mGy) cumulative protracted radiation doses, large size and prospective cohort design. We utilised a comprehensive occupational dosimetry with estimated absorbed doses specific to the eye lens (discussed at greater length in Appendix B). Although a substantial proportion of the estimated cumulative occupational dose is derived from questionnaires (21), the dosimetry has been subjected to extensive validation, in particular *via* chromosome aberrations detected using fluorescence *in situ* hybridisation (FISH) (35). The large number of covariates evaluated and *a priori* decisions about the data analysis is another strength, with adjustment for several factors that have been associated with cataract, including diabetes, smoking, obesity (via BMI), and solar UVR. The comprehensive work history, demographic, lifestyle and medical factors evaluated facilitated analysis of modifying effects of these variables on the radiation dose response. Another novelty and strength of the present study is the analysis of time-dependent doses accumulated in windows of time since exposure and age at exposure, something that has only rarely been attempted for any health endpoint in relation to radiation or other important exposures.

Despite the large size of the population of medical workers and broad-based assessment of covariates our study had several limitations. All clinical disease outcomes and at least some of the exposure data were ascertained solely by questionnaire and not validated. It might be expected that there would be inter-subject variation (e.g., varying with age and employment status) in the propensity to remember a medical diagnosis of cataract. However, the population of radiologic technologists reported here is medically literate, so that self-reporting of diagnoses for the various ocular endpoints, and medical risk factors such as diabetes should be reasonably reliable. All analyses adjust for age, which is the timescale of the Cox proportional hazards models used here, and which should largely eliminate the major risk factor for propensity to mis-remember diagnostic information. Another weakness is the lack of information on cataract subtype. Of some concern is the discrepancy between the findings for cataract history and cataract surgery, where risks for latter were somewhat lower and generally not significant (Table 3); however, the risks for cataract surgery were

statistically consistent with risks for cataract history. We did not have information on other important factors, such as ocular trauma, which is a well-known risk factor for cataract induction (4) and that frequently requires diagnostic radiographs, raising the possibility of confounding by indication, although ocular trauma is relatively rare (36) and thus would not be expected to be frequent enough to materially confound the trend observed here. Another weakness is that, as with many occupational studies, cohort members had to survive to answer the second questionnaire and be free of cataract at that point. However, this degree of selection will not necessarily bias our analysis, since everyone had to survive to answer a questionnaire, and all risk was assessed conditional on that. Follow-up for each endpoint was censored at the date of the last informative questionnaire answered. The plausible assumption was made that censoring was non-informative with respect to the endpoint (cataract history, cataract surgery) being considered.

In summary, the present large occupational study of low dose and low dose-rate radiation exposure found evidence of excess risks of self-reported history of cataract at eye-lens absorbed dose < 100 mGy. The risks for self-reported history of cataract, and their variation with time since exposure and age at exposure, are consistent with those seen in studies of groups exposed to higher doses and dose rates. Elevated risks were observed at doses substantially lower than the threshold of 500 mGy suggested by the ICRP (8), with implications for radiological protection. In particular, our findings, if confirmed, need to be considered as interventional radiologists may receive eye-lens doses well over the 100 mGy value (37, 38). Future studies should assess cataract risk in other radiation-exposed occupational groups with clinically-ascertained diagnosis of cataract by cataract type, medical record validation of cataract surgery, well-validated dosimetry and high-quality data on relevant lifestyle, environmental, and medical risk factors, to determine if our findings that cataract is inducible by very low doses of radiation would be confirmed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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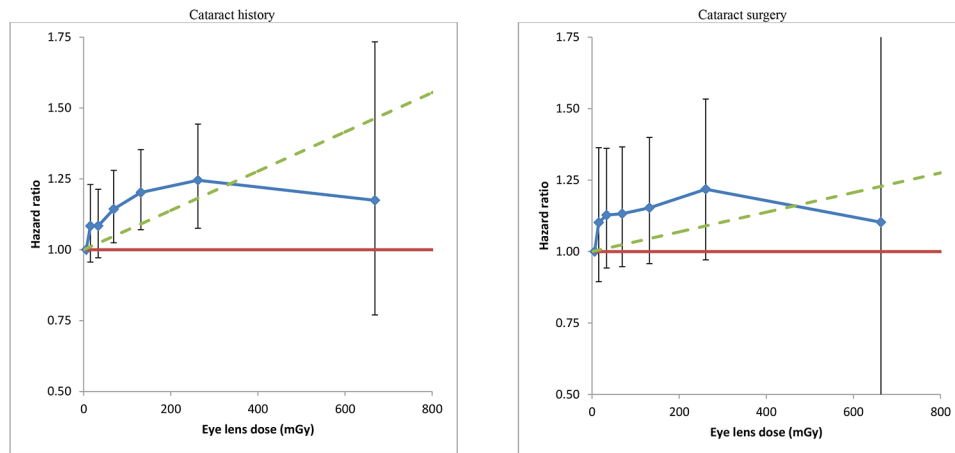


Figure 1. Adjusted hazard ratios for self-reported history of diagnosis of cataract and self-reported cataract surgery in US radiologic technologists in relation to cumulative eye-lens absorbed dose from occupational exposures (+95% CI).

^aRisks are evaluated using a Cox model with age as timescale with stratification by sex and race, and with adjustment to the baseline hazard for diabetes, body mass index (BMI), smoking status (current smoker/ex-smoker/never smoker, numbers of cigarettes/day, age stopped smoking), each ascertained at the baseline survey, and cumulative UVB radiant exposure, ascertained in the course of follow-up. For each endpoint (cataract, cataract extraction) follow-up is restricted to those persons eligible for study (no record of radiotherapy or disease at baseline, unambiguous status at end of follow-up etc) and for cataract surgery the subject had to be free of cataract at the baseline questionnaire (see Methods). The cumulative eye-lens absorbed dose groups used were 0-9, 10-19, 20-49, 50-99, 100-199, 200-499, 500 mGy, the first of these used as the reference group (relative risk=1). For cataract surgery the baseline hazard was adjusted by 1 years since baseline questionnaire < 5 years, and excess risk was limited to 5 years after baseline questionnaire.

Table 1.

Numbers of cases and person-years of follow-up for technologists self-reporting history of diagnosis of cataract and self-reporting cataract surgery in US radiologic technologists in relation to non-radiation risk factors.

The hazard ratios were derived using univariate Cox proportional hazards models with age as the timescale. In all cases the heterogeneity in hazard ratio was significant with $p < 0.001$.

Characteristic	Cataract history			Cataract surgery		
	Cases	Person years	Hazard ratio ^d	Cases	Person years	Hazard ratio ^d
Total	12,366	832,479		5509	888,420	
Sex						
Male	2686	175,730	1 (reference)	1249	186,602	1 (reference)
Female	9650	656,749	1.26 (1.21, 1.31)	4260	701,818	1.22 (1.14, 1.30)
Racial/ethnic group						
White	11,735	792,185	1 (reference)	5249	845,160	1 (reference)
Black	346	20,666	0.82 (0.74, 0.91)	141	22,522	0.68 (0.57, 0.80)
Other	255	19,628	0.74 (0.66, 0.84)	119	20,737	0.78 (0.65, 0.93)
Diabetes at baseline						
None	11,256	794,319	1 (reference)	4982	846,085	1 (reference)
Missing	454	24,066	0.94 (0.85, 1.03)	205	25,565	0.93 (0.81, 1.07)
Diabetes	626	14,094	2.18 (2.01, 2.36)	322	16,771	2.05 (1.83, 2.30)
BMI (kg/m²) at baseline						
18.5-24.9 (normal)	5399	425,495	1 (reference)	2333	450,427	1 (reference)
Missing	265	17,612	0.99 (0.88, 1.12)	131	18,922	1.09 (0.92, 1.30)
0-18.4	138	11,197	1.10 (0.93, 1.30)	56	11,774	1.07 (0.82, 1.40)
25.0-29.9	4211	248,530	1.08 (1.04, 1.13)	1962	267,464	1.11 (1.05, 1.18)
30.0	2323	129,645	1.26 (1.20, 1.32)	1027	139,833	1.29 (1.20, 1.39)
Baseline smoking status						
Never smoked	6269	478,669	1 (reference)	2702	507,248	1 (reference)
Missing smoking status	102	6,155	0.83 (0.69, 1.01)	55	6726	0.88 (0.68, 1.16)
Former smoker	4356	247,719	1.04 (1.00, 1.08)	2027	267,868	1.04 (0.99, 1.11)
Current smoker	1609	99,937	1.18 (1.12, 1.25)	725	106,578	1.30 (1.20, 1.41)

Characteristic	Cataract history			Cataract surgery		
	Cases	Person years	Hazard ratio ^a	Cases	Person years	Hazard ratio ^a
Baseline smoking quantity (cigarettes/day)						
Missing/never smoker	6612	499,425	1 (reference)	2868	529,847	1 (reference)
0-9	970	64,105	0.96 (0.90, 1.02)	434	68,511	0.94 (0.85, 1.05)
10-19	1810	117,129	1.04 (0.99, 1.10)	841	125,119	1.10 (1.02, 1.19)
20-29	2038	111,527	1.13 (1.08, 1.19)	928	120,690	1.15 (1.06, 1.23)
30-39	515	25,013	1.19 (1.08, 1.30)	243	27,271	1.28 (1.12, 1.45)
40-49	294	12,237	1.24 (1.11, 1.40)	147	13,524	1.35 (1.14, 1.59)
50-59	51	1550	1.56 (1.18, 2.05)	25	1752	1.60 (1.08, 2.37)
60	46	1493	1.27 (0.95, 1.69)	23	1706	1.35 (0.90, 2.04)
Baseline age at stopping smoking (years)						
Never stopped/never smoked	6602	501,662	1 (reference)	2875	532,153	1 (reference)
0-19	54	5398	0.98 (0.75, 1.27)	13	5610	0.57 (0.33, 0.98)
20-29	1073	90,257	0.96 (0.90, 1.02)	416	95,444	0.91 (0.82, 1.01)
30-39	1359	98,172	1.08 (1.02, 1.15)	580	104,309	1.07 (0.98, 1.17)
40-49	1644	97,094	1.16 (1.10, 1.23)	732	104,333	1.23 (1.14, 1.34)
50-59	1216	34,374	1.10 (1.03, 1.17)	675	39,815	1.24 (1.14, 1.35)
60	388	5522	1.11 (1.00, 1.23)	218	6755	0.95 (0.83, 1.10)
Birth year						
<1920	121	750	2.11 (1.67, 2.66)	26	892	0.13 (0.08, 0.20)
1920-1929	912	10,227	1.06 (0.97, 1.17)	439	13,230	0.32 (0.28, 0.37)
1930-1939	3203	72,202	0.86 (0.81, 0.90)	2007	88,490	0.64 (0.59, 0.69)
1940-1949	5385	282,846	1 (reference)	2225	307,795	1 (reference)
1950	2,715	466,455	1.16 (1.10, 1.23)	812	478,014	1.33 (1.20, 1.48)

^a *p*-values of heterogeneity (assessed via likelihood ratio test) are all *p*<0.001.

Table 2.
Numbers of cases and person-years of follow-up for technologists self-reporting history of diagnosis of cataract and self-reporting cataract surgery in US radiologic technologists in relation to cumulative eye-lens absorbed dose from occupational exposures (non time-varying).

The hazard ratios were derived using a Cox proportional hazards model with age as timescale, unadjusted for any other covariate.

Eye-lens absorbed dose (mGy)	Cataract history			Cataract surgery		
	Cases	Person years	Hazard ratio ^a	Cases	Person years	Hazard ratio ^a
<10.0	415	43,386	1 (reference)	174	45,096	1 (reference)
10.0-19.9	948	125,145	1.09 (0.97, 1.22)	345	129,319	1.00 (0.83, 1.20)
20.0-49.9	3874	363,712	1.11 (1.00, 1.23)	1566	381,068	1.11 (0.95, 1.30)
50.0-99.9	4027	217,756	1.15 (1.04, 1.27)	1853	237,159	1.22 (1.05, 1.43)
100.0-199.9	2302	71,356	1.15 (1.03, 1.27)	1212	82,074	1.27 (1.08, 1.49)
200.0-499.9	722	10,774	1.32 (1.17, 1.50)	347	13,231	1.17 (0.97, 1.41)
500.0	48	350	1.76 (1.29, 2.40)	12	473	0.61 (0.33, 1.10)

^a *p*-values of heterogeneity (assessed via likelihood ratio test) are all *p*<0.001.

Table 3.
Occupational radiation risks of self-reported history of diagnosis of cataract and self-reported cataract surgery, in relation to maximum cumulative eye lens absorbed dose.^a

Dose range	Endpoint	Cases	EHR / mGy x 10 ³ (+95% CI)	p-value
0-100 mGy	Cataract history	9264	1.16 (0.11, 2.31)	0.030
	Cataract surgery	3938	0.39 (-1.15, 2.22)	0.638
0-200 mGy	Cataract history	11,566	1.07 (0.47, 1.72)	<0.001
	Cataract surgery	5150	0.17 (-0.59, 1.05)	0.675
Unrestricted	Cataract history	12,336	0.69 (0.27, 1.16)	<0.001
	Cataract surgery	5509	0.34 (-0.19, 0.97)	0.221

^aRisks are evaluated using a Cox model with age as timescale, with stratification by sex and race and birth year (by decade <1900, 1900-1909, ..., 1950-1959, 1960), and with adjustment to the baseline hazard for diabetes, body mass index (BMI), smoking status (current smoker/ex-smoker/never smoker, numbers of cigarettes/day, age stopped smoking), each ascertained at the baseline survey, and cumulative UVB radiant exposure, ascertained in the course of follow-up. For each endpoint (cataract, surgical cataract extraction) follow-up is restricted to those persons eligible for study (no record of radiotherapy or disease at baseline, unambiguous status at end of follow-up (with both fact and year of self-reported diagnosis known) etc)(see Methods). For cataract surgery the baseline hazard was adjusted by 1 years since baseline questionnaire < 5 years, and excess risk was limited to 5 years after baseline questionnaire.

Table 4.

Excess hazard ratio (EHR) of self-reported history of diagnosis of cataract and self-reported cataract surgery in US radiologic technologists in relation to cumulative eye-lens absorbed dose from occupational exposures (+95% CI), and modifications by various lifestyle and environmental risk factors.

Other notes are as for Table 3.

	Cataract history		Cataract surgery		Heterogeneity p-value
	Cases	EHR/mGy x 10 ³ (+95% CI)	Cases	EHR/mGy x 10 ³ (+95% CI)	
Sex					
Males	2686	0.25 (-0.35, 1.02)	1249	0.19 (-0.60, 1.26)	0.688
Female	9650	0.91 (0.39, 1.50)	4260	0.42 (-0.22, 1.19)	
Racial group					
White	11,735	0.72 (0.31, 1.23)	5,249	0.35 (-0.17, 0.94)	0.358
Black	346	-1.11 (-2.43, 1.14)	141	-1.44 (-3.09, 1.75)	
Other	255	0.31 (-1.95, 4.69)	119	-0.75 (-2.08, 2.92)	
Age attained					
age < 50	655	6.29 (0.59, 15.40)	166	-4.09 (-8.18 ^a , 3.08)	0.542
age 50-59	3570	1.11 (-0.11, 2.54)	1013	0.73 (-1.36, 3.46)	
age 60-69	5741	1.01 (0.32, 1.79)	2404	0.53 (-0.43, 1.67)	
age 70	2370	0.29 (-0.19, 0.89)	1926	0.25 (-0.35, 1.00)	
Body mass index (BMI)					
BMI < 18.5 (underweight)	138	0.87 (0.35, 1.45)	56	0.36 (-0.30, 1.13)	0.893
BMI 18.5-24.9 or unknown (normal)	5664	-0.64 (-2.08, 1.51)	2464	1.03 (-2.23, 5.70)	
BMI 25.0-29.9 (overweight)	4211	0.69 (0.19, 1.25)	1962	0.22 (-0.41, 0.98)	
BMI ≥ 30 (obese)	2323	0.36 (-0.27, 1.09)	1027	0.54 (-0.35, 1.64)	
Diabetes					
No diabetes/missing	11,710	0.85 (0.40, 1.34)	5187	0.46 (-0.10, 1.12)	0.063
Diabetes	626	-0.95 (-1.57, 0.03)	322	-0.96 (-1.93, 0.53)	
Baseline smoking status					
Unknown smoking status	102	3.63 (0.28, 11.14)	55	2.56 (-1.71, 12.82)	0.722
Never smoked	6269	0.74 (0.19, 1.36)	2702	0.53 (-0.19, 1.41)	

	Cataract history			Cataract surgery		
	Cases	EHR/mGy x 10 ³ (+95% CI)	Heterogeneity <i>p</i> - value	Cases	EHR/mGy x 10 ³ (+95% CI)	Heterogeneity <i>p</i> -value
Former smoker	4356	0.76 (0.17, 1.44)		2027	0.20 (-0.46, 1.04)	
Current smoker	1609	-0.04 (-0.86, 0.99)		725	0.05 (-1.07, 1.54)	
Baseline smoking quantity (cigarettes/day)						
Missing/never smoker	6612	0.81 (0.28, 1.42)	0.605	2868	0.60 (-0.11, 1.45)	0.260
0-9	970	0.47 (-0.40, 1.53)		434	0.13 (-1.09, 1.69)	
10-19	1810	0.96 (0.21, 1.83)		841	0.82 (-0.34 ^a , 2.01)	
20-29	2038	0.61 (-0.05, 1.37)		928	-0.07 (-0.83, 0.85)	
30-39	515	-0.05 (-1.02, 1.14)		243	-0.78 (-1.55, 0.69)	
40-49	294	-0.18 (-1.31, 1.32)		147	-0.77 (-2.52, 1.40)	
50-59	51	0.91 (-1.83, 5.10)		25	-0.70 (-3.72, 4.60)	
60	46	-0.76 (-2.03, 1.83)		23	-2.49 (-3.48, 0.25)	
Baseline age at stopping smoking (years)						
Never stopped/never smoked	6602	0.84 (0.30, 1.46)	0.282	2875	0.58 (-0.12, 1.35 ^a)	0.347
0-19	54	0.67 (-2.53, 5.84)		13	-3.79 (-6.97 ^a , 1.98)	
20-29	1073	0.27 (-0.78, 1.55)		416	0.52 (-0.81, 2.43)	
30-39	1359	1.01 (0.14, 2.02)		580	0.64 (-0.55, 2.11)	
40-49	1644	1.03 (0.21, 1.96)		732	0.31 (-0.64, 1.43 ^a)	
50-59	1216	0.35 (-0.33, 1.18)		675	0.13 (-0.78, 1.25)	
60	388	0.02 (-0.71, 0.96)		218	-0.64 (-1.54 ^a , 0.51)	
Birth year						
<1920	121	0.10 (-0.68, 2.33)	0.507	26	>1000 ^b (<-1000 ^a , >1000 ^a)	0.084 ^b
1920-1929	912	0.37 (-0.28, 1.25)		439	-0.17 ^b (-0.79, 0.85)	
1930-1939	3203	0.60 (-0.06, 1.36)		2007	0.65 ^b (-0.16, 1.64)	
1940-1949	5385	1.10 (0.27, 2.04)		2225	0.46 ^b (-0.61, 1.75)	
1950	2715	1.69 (-0.06, 3.78)		812	-1.17 ^b (-3.23, 1.71)	
Cumulative UVB radiant exposure						
UVB unknown	1713	0.98 (0.08, 2.09)	0.790	867	1.47 (0.33, 2.91)	0.067
UVB < 0.075 MJ cm ⁻²	10,016	0.66 (0.21, 1.16)		4190	-0.01 (-0.51, 0.59)	

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	Cataract history			Cataract surgery		
	Cases	EHR/mGy x 10 ³ (+95% CI)	Heterogeneity <i>p</i> - value	Cases	EHR/mGy x 10 ³ (+95% CI)	Heterogeneity <i>p</i> -value
UVB 0.075-0.10 MJ cm ⁻²	682	0.50 (-0.19, 1.35)		444	0.53 (-0.35, 1.64)	
UVB 0.10 MJ cm ⁻²	5	2.59 (-1.54, 13.85)		8	2.03 (-1.84, 10.77)	
Total	12,336	0.69 (0.27, 1.16)	<0.001 ^c	5509	0.34 (-0.19, 0.97)	0.221 ^c

^aWald-based confidence intervals.

^bIndications of non-convergence.

^c*P*-value of improvement in fit over null model (with no trend in dose), assessed via likelihood ratio test.

Table 5.
Excess hazard ratio (EHR) of self-reported history of diagnosis of cataract by time since exposure^a and age at exposure^b in US radiologic technologists in relation to cumulative eye-lens absorbed dose from occupational radiation exposures (+95% CI).

Other notes are as for Table 3.

	EHR/mGy x 10 ³ (+95% CI)	Heterogeneity <i>p</i> -value
Risk by time since exposure ^a		
5-9 years since exposure	8.71 (-1.77, 20.34)	0.323
10-14 years since exposure	-0.91 (-6.81, 5.74)	
15 years since exposure	0.66 (0.23, 1.14)	
Risk by age at exposure ^b		
age at exposure <30 years	0.91 (0.35, 1.53)	0.362
age at exposure 30-49 years	0.42 (-0.40, 1.30)	
age at exposure ≥ 50 years	-0.47 (-3.20, 2.86)	

^a time since exposure is the length of the interval (in years) between when radiation exposure occurs for the individual and the time at risk.

^b age at exposure is the age (in years) at which the individual is exposed to radiation.

Table 6.

Risks for cataract in radiation-exposed cohorts

Cohort	Dose (mGy), mean (range)	Ascertainment	Endpoint	Cases	Excess hazard ratio $\text{mGy}^{-1} \times 10^3$ or excess odds ratio $\text{mGy}^{-1} \times 10^3$ (95% CI)
					Cataract history
Present study	56 (0-1514)	Questionnaire	Cataract surgery	12,366	0.69 (0.27, 1.16) 0.34 (-0.19, 0.97)
Swedish skin haemangioma (34)	400 (0-8400)	LOCS I	Cortical Posterior subcapsular	111 ^a 17 ^a	0.50 (0.15, 0.95) 0.49 (0.07, 1.08)
Japanese atomic bomb survivor AHS (39)	522 (0-4940) ^b	LOCS II	Cortical Posterior subcapsular Nuclear opacity	618 ^c 214 ^c 415 ^c	0.30 (0.10, 0.53) ^d 0.44 (0.19, 0.73) ^d 0.07 (-0.11, 0.30) ^d
Japanese atomic bomb survivor AHS cataract surgery (10)	500 (0-5140) ^b	Surgical removal	Nuclear colour All cataract removal	358 ^c 1028	0.01 (-0.17, 0.24) ^d 0.32 (0.17, 0.52) ^{d, e}
Icelandic airline pilots (36)	NA (0-48)	WHO	Nuclear Cortical Posterior subcapsular	71 102 32	20 (0, 30) <0 (<0, >0) <0 (<0, >0)
Chernobyl recovery worker (12)	NA (0->1095)	Merriam-Focht	Non-nuclear stage 1-5 Posterior subcapsular stage 1 Nuclear	3369 ^{4,f} / _{274^g} 2781 ^{4,f} / _{252^g} 382 ^{4,f} / _{113^g}	0.65 (0.18, 1.30) 0.42 (0.01, 1.00) 0.07 (-0.44, 1.04)
US Radiologic technologist (19)	28.1 ^h (0->60.1)	Self-reported incident and removal	All cataract stage 1-5 All cataract removal	3751 ^{4,f} / _{384^g} 2382 ^g / _{384^f}	0.70 (0.22, 1.38) 2.0 (-0.7, 4.7)
Finnish interventional radiologists (40)	60 (10-304)	LOCS II	Cortical or posterior excluding nuclear All opacity (excluding nuclear color)	7 ^c 15 ^c	4 (-20, 28) 13 (-2, 28)

Acronyms: AHS = Adult Health Study; LOCS = Lens Opacities Classification System; WHO=World Health Organization

^a summed over cataracts in left and right eyes.

^b dose in mSv.

^c all cases with LOCS II grade I and above.

^d EOR $\text{mSV}^{-1} \times 10^3$.

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

^f prevalent cataract.

^g incident cataract.

^h median dose.

ⁱ surgically removed cataract.

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