Journal of Radiation Research, Vol. 62, No. 1, 2021, pp. 67–72
doi: 10.1093/jrr/rraa073
Advance Access Publication: 2 October 2020

Journal of Radiation Research

OXFORD

Lens opacity prevalence among the residents in high natural background radiation area in Yangjiang, China

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(Received 3 December 2020; revised 3 April 2020; editorial decision 28 July 2020)

ABSTRACT

The aim of the study was to evaluate the risk and threshold doses of lens opacity among residents exposed to low-dose radiation. Residents aged ≥45 years were recruited from a high natural background radiation (HNBR) area in Yangjiang City and a control area selected from nearby Enping City. Lens opacities (LOPs) were classified according to the Lens Opacities Classification System (LOCS) III system. Face-to-face interviews were conducted to collect information on lifestyles, migration and medical history. Life-time cumulative doses were estimated using gender, age, occupancy factors and environmental radiation doses received indoors and outdoors. Logistic regression analyses were conducted to estimate the dose response and determine thresholds. In the HNBR area, among 479 study participants, 101 (21.1%), 245(51.1%) and 23 cases (4.8%), respectively, of cortical, nuclear and posterior subcapsular (PSC) LOPs were found. In the control area, those types of LOPs were identified among 58 cases (12.6%), 206 cases (51.2%) and 6 cases (1.3%) of 462 examinees, respectively. Cumulative eye lens dose was estimated to be 189.5 ± 36.5 mGy in the HNBR area. Logistic analyses gave odds ratios at 100 mGy of 1.26 [95% confidence interval (CI) 1.00–1.60], 0.81 (95% CI 0.64–1.01) and 1.73 (95% CI 1.05–2.85) for cortical, nuclear and PSC LOPs, respectively. For cortical LOPs, a logistic analysis with a threshold dose gave a threshold estimate of 140 mGy (90% CI 110–160 mGy). The results indicated that population exposed to life-time, low-dose-rate environmental radiation was at an elevated risk of cortical and PSC LOPs. A statistically significant threshold dose was obtained for cortical LOPs and no threshold dose for PSC LOPs.

Keywords: lens opacity; high natural background radiation; threshold dose; low-dose

INTRODUCTION

It is generally believed that ionizing radiation causes eye lens opacities (LOPs), especially the one located in the posterior subcapsular (PSC) position, and leads to visual impairment (cataract) when the exposure exceeds a certain dose [1]. To decide the dose limits for LOPs and cataracts, the 1990 recommendations of the International

Commission on Radiological Protection (ICRP) used a threshold dose of 0.5–2 Gy for LOPs and 5 Gy for cataracts in the case of single acute (or brief) exposure. For protracted exposure, including fractionated and prolonged exposures, the threshold was 5 Gy for LOPs and 8 Gy for cataracts [1]. Note that dose thresholds for detectable LOPs and vision-impairing cataracts should be considered separately because of the lack of direct mechanistic evidence that all minor LOPs progress to cataracts with time [2].

In recent years, lower thresholds were suggested by a number of new studies [3], including more recent analyses of atomic bomb survivor data [4, 5], Chernobyl liquidator worker studies [6] and a cohort study of radiologic technologists [7, 8]. ICRP Publication 118 reviewed those recent studies and concluded that studies with long follow-up periods indicated a threshold dose of ~0.5 Gy with 90 or 95% confidence intervals (CIs) including zero dose for cataracts induced by acute exposure. For protracted exposures, an accumulated dose threshold of 0.35 Sv is indicated from the Chernobyl liquidator worker study for Stage 1 (early) PSC and cortical opacities [2]. Regarding chronic irradiation, there have been studies of diagnostic radiation technologists [7, 8], commercial pilots and astronauts [9, 10], Mayak workers [11], residents of the Techa riverside villages [12] and residents of ^{60}Co-contaminated buildings in Taiwan, China [13]. These studies are not generally as informative about threshold doses, but all of them are consistent in showing some degree of risk at low doses. Based on many epidemiological studies, ICRP Publication 118 significantly reduced the threshold dose for cataract and the personal eye-lens dose limits for occupational exposure [2].

As pointed out by ICRP Publication 118 [2], epidemiological and biological studies have provided inconsistent evidence for the association between the risk of LOPs and chronic low-dose-rate exposure, and the uncertainties raised from epidemiological findings make it difficult to draw any conclusions regarding the presence of thresholds for such an association. Therefore, better techniques for detecting and quantifying, as well as better dosimetry, may be factors that contributed to more recent findings of radiation cataract risk at low exposures. Continued study of the the risk of LOPs as a result of chronic low dose exposure may lead to a more precise estimate of any threshold.

The Yangjiang area in Guangdong Province, China is known for its high natural background radiation (HNBR). The average annual doses from natural external radiation in the HNBR area and control area were estimated to be 2.10 and 0.77 mSv y^{-1}, respectively [14, 15]. The health survey in Yangjiang area and the control area was started in 1972. Since then, a long-term mortality follow-up study and other epidemiological studies have been conducted [16, 17]. In a cross-sectional study conducted in the early 1970s, the prevalence rate of 'unknown cause' cataract in the HNBR area was statistically higher than that in the control area (119/2733 vs 57/3220), and the location of opacities were found in the anterior or posterior lens capsule [18]. In a previous study by our group [19], the odds ratios (ORs) comparing LOP prevalence rates among residents living in the HNBR area of Yangjiang and the control area were 2.93 (95% CI 1.19–7.17),1.51 (95% CI 0.15–15.24), 2.93 (95% CI 1.20–7.17) and 2.35 (95% CI 0.59–9.42) for all, cortical, nuclear and PSC LOPs, respectively. But radiation dose was not estimated and no dose–response analysis was conducted in the previous study.

The purpose of present study was to quantify the risk of LOPs by anatomical location, i.e. cortical, nuclear and PSC, in association with life-time exposure to naturally high background radiation, and to elucidate the presence of a dose threshold if any.

SUBJECTS AND METHODS

Subjects

Residents in two towns with the highest environmental dose-rate in the HNBR of Yangjiang City were recruited for the present study. The control group was chosen from three towns in Enping City. The two selected cities were neighboring, with similar altitude and latitude. All of the selected subjects were farmers, they shared the same labor habits and we considered that the amount of ultraviolet rays exposure was same. The annual dose of external radiation from environmental γ-ray exposure in the HNBR and control area were 1.87 and 0.44 mSv·y^{-1} on average, respectively. We excluded those aged <45 years old since the cumulative radiation dose was expected to be too low, and the risk of LOPs might be too small to detect. Written informed consent was obtained from every participant after explaining the nature and possible consequences of the study. To collect information on potential confounding factors, a face-to-face interview using a structured questionnaire was conducted. Questions included age, sex, smoking and drinking habits, birthplace and age of marriage, medical history including diabetes mellitus and past and current medication including corticosteroid use (≥6 months).

Eye dosimetry

Individual lens dose from the HNBR was estimated on the bases of outdoor and indoor environmental dose-rates, and gender- and age-specific occupancy factors. Environmental dose-rates, and gender- and age-specific occupancy factors were obtained from previous studies [15, 20, 21]. For most females, birthplace may be not consistent with place of residence. Therefore, history of migration was considered in this study. The formula to calculate the annual absorbed lens dose for each individual $D_{\text{individual}}\,\text{y}^{-1}$ (mGy) was as follows:

$$\begin{aligned} D_{\text{individual}}\text{y}^{-1} = [(&D_{\text{main bedroom}}\text{y}^{-1} - CR_{\text{indoor}}\text{y}^{-1}) \\ &\times OF_{\text{main bedroom}} + (D_{\text{other rooms}}\text{y}^{-1} - CR_{\text{indoor}}\text{y}^{-1}) \\ &\times OF_{\text{other rooms}} + (D_{\text{outdoor}}\text{y}^{-1} - CR_{\text{outdoor}}\text{y}^{-1}) \times OF_{\text{outdoor}}] \times CF \end{aligned} \quad (1)$$

where $D_{\text{main bedroom}}$ y^{-1}, $D_{\text{other rooms}}$ y^{-1}, and D_{outdoor} y^{-1} are annual doses for the main bedroom, the other rooms including sitting-room and kitchen, and the outdoors, respectively. Outdoors includes public places, such as courtyard, lane and street, and water-well, and farmland in a corresponding hamlet; CR_{indoor} y^{-1} and CR_{outdoor} y^{-1} are indoor and outdoor annual cosmic ray doses, respectively; $OF_{\text{main bedroom}}$, $OF_{\text{other rooms}}$, and OF_{outdoor} are the occupancy factors for the main bedroom, the other rooms including sitting-room and kitchen, and the outdoors, respectively.

CF is the conversion factor for air-kerma to organ-specific absorbed dose, which was calculated from air-kerma to fluence, then from fluence to organ-specific dose, as presented in ICRP Publication 116 [22]. The irradiation field was assumed to be mainly from thorium, the mean

Table 1. Demographic characteristics in Yangjiang eye lens opacity study

	HNBR area	Control area	*P*-value
n	479	462	
Age (years)	67.8 ± 10.0	63.8 ± 10.0	<0.001
Sex (female)	224 (46.8%)	242 (52.4%)	0.085
Smoking (yes/never)	114 (23.8%)	166 (35.9%)	<0.001
Drinking (yes/never)	81 (16.9%)	64 (13.9%)	0.194
History of diabetes mellitus	-	6 (1.3%)	0.012
History of corticosteroid use	2 (0.4)	3 (0.6%)	0.657
Lifetime cumulative dose (mGy)	189.5 ± 36.5	36.5 ± 5.8	<0.001

energy was assumed to be 0.64 MeV and the irradiation geometry to be isotropic based on ICRP publication 74 [23]. The CF was finally estimated to be 0.868 for eye lens, and the factor was increase by 30 and 10% for infants (<1 year old) and children aged 1–14 years, respectively.

Eye examination and cataract grading

A single registered ophthalmologist who was blinded as to the exposure status of examinees conducted eye examinations for all participants using a portable slit-lamp. LOPs were classified into the following three types based on the anatomical location: nuclear, cortical and PSC. All three types of LOPs could appear simultaneously in each eye. LOP grading was made based on the Lens Opacities Classification System (LOCS) III grading guideline [24]. Reference slides were used to assist the ophthalmologist in identifying nuclear, cortical and PSC LOPs, and in determining the grade/stage. LOPs were dichotomized as the presence (stage≥1) or absence of LOPs in either the left or right eye.

Statistical analysis

In the analysis, current-smokers and ex-smokers (very few, if any) were treated as smokers; drinking was defined as any kind of alcohol consumption in the past 12 months, including beer, wine and spirits. Student's *t*-test was used to calculate the *P*-value for the comparison of the average of continuous variables between groups. The chi-square or Fisher's exact test was used to compare the distribution of categorical variables. All tests were two-sided. *P*-value < 0.05 was considered to be statistically significant. The ORs of nuclear, cortical and PSC LOPs in the HNBR compared with the control area were estimated with logistic regression models. Generally accepted risk factors for cataracts, i.e. age, gender, smoking and drinking status, were adjusted in the statistical model. Although history of diabetes and corticosteroid use were collected and known to be associated with LOPs, they affected too few people to be included in the analysis (see Table 1).

A threshold dose was determined following the methodology used in an A-bomb survivors study reported by Nakashima *et al.* [4]. Briefly, radiation dose D was treated as $(D-d_0)$ if $D \geq d_0$, and zero if $D < d_0$. Here, d_0 is a trial threshold dose. Changing the value d_0, the best fitting value was determined on the basis of the likelihood ratio statistic (LRS). The threshold dose estimate was the value that attained the minimum LRS, which is −2 times log-likelihood, the best fit in terms of threshold dose. A threshold would be deemed significant if the LRS (i.e. 2 x (ln[likelihood with threshold at d_0]—ln[likelihood with threshold at 0])) is >2.71, the 90% point of the chi-squared random variable with 1 degree of freedom. The 90% CIs are likelihood based. All analyses were carried out using STATA 14.0.

RESULTS

Population characteristics

Excluding 59 persons [4 persons without sufficient data, 4 patients with glaucoma, 2 with atrophy of the eyeball, 1 with trauma of the eyeball, 48 with a history of cataract surgery (33 of whom were subjects from the control area and 15 from HNBR)], there were 941 residents available for statistical analysis, 479 persons from the HNBR area and 462 in the control area. The demographic characteristics of these residents are shown in Table 1. Smoking includes 37 ex-smokers (10 persons from the HNBR area and 27 in the control area) in the present study. The cumulative lens dose ranged from 68.4 to 310.4 mGy, with means of 189.5 ± 36.5 mGy for HNBR area residents, and ranged from 22.1 to 53.9 mGy, with means of 36.5 ± 5.8 mGy for control area inhabitants.

Risk assessment of LOPs

Both left and right eyes were examined for each subject. If a subject's LOPs in the right and left eyes differed in grade of opacity, the worse grade was used for analysis. In the HNBR area, among 479 study participants, cortical, nuclear and PSC LOPs were found 101 (21.1%), 245 (51.1%) and 23 (4.8%) cases, respectively. In the control area, those types of LOPs were identified among 58 (12.6%), 206 (51.2%) and 6 (1.3%) cases of 462 examinees, respectively.

The result obtained from analyses using a logistic regression model is summarized in Table 2. In these analyses, the following variables were included in the model: sex, age, smoking, drinking and radiation dose. History of diabetes mellitus and corticosteroid use were not included as factors in the model due to the very small sample size (for diabetes mellitus, 6 from the control area; with corticosteroid use, 2 persons from the HNBR and 3 persons from the control area). The risk of each type of LOP increased with age, with ORs 1.08 (95% CI 1.06–1.10, $P < 0.001$) for cortical LOPS, 1.18 (95% CI 1.16–1.21, $P < 0.001$) for nuclear LOPs and 1.10 (95% CI 1.05–1.15, $P < 0.001$) for PSC LOPs. Smoking was found to be a significant risk factor for PSC, with an OR of 4.62 (95% CI 1.55–13.81, $P = 0.006$), but not for cortical and nuclear LOPs, with ORs 1.16 (95% CI 0.69–1.97, $P > 0.05$) for cortical LOPs and 1.44 (95% CI 0.91–2.27, $P > 0.05$) for nuclear

Table 2. The results of multiple logistic regression analyses

Variable	OR	95% CI	*P*-value
Cortical LOPs			
Dose (at 100 mGy)	1.26	1.00–1.60	0.048
Age (years)	1.08	1.06–1.10	<0.001
Sex (male/female)	1.31	0.83–2.07	0.245
Smoking (yes/never)	1.16	0.69–1.97	0.575
Drinking (yes/never)	1.00	0.54–1.69	0.873
Nuclear LOPs			
Dose (at 100 mGy)	0.81	0.64–1.01	0.061
Age (years)	1.18	1.16–1.21	<0.001
Sex (male/female)	1.26	0.83–1.91	0.282
Smoking (yes/never)	1.44	0.91–2.27	0.122
Drinking (yes/never)	0.908	0.567–1.452	0.686
PSC LOPs			
Dose (at 100 mGy)	1.73	1.05–2.85	0.032
Age (years)	1.10	1.05–1.15	<0.001
Sex (male/female)	1.43	0.50–4.05	0.515
Smoking (yes/never)	4.62	1.55–13.81	0.006
Drinking (yes/never)	0.48	0.15–1.58	0.226

LOPs. After adjusting for age, sex, smoking and drinking, a statistically significant increase of risk in association with cumulative radiation dose was observed for cortical LOPs (OR/100 mGy = 1.26, 95% CI 1.00–1.60, $P = 0.048$) and PSC LOPs (OR/100 mGy = 1.73, 95% CI 1.05–2.85, $P = 0.032$).

Threshold dose

We tried to find dose–response thresholds for cortical and PSC LOPs, which were statistically correlated with dose, using logistic regression models. In Figs 1 and 2, solid lines show the −2 times log-likelihood curves. The threshold dose for cortical LOPs was estimated to be 140 mGy, which corresponds to the minimum value of −2 times log-likelihood in Fig. 1. The 90% CI of the threshold dose consisted of the d_0 values for which −2 times the log-likelihood equalled the minimum log-likelihood value plus 2.71 (i.e. the upper 10% value of the chi-square distribution with one degree of freedom, $\chi^2_{(1)}(90) = 2.71$). The 90% CIs of the thresholds were 110–160 mGy for cortical LOPs. The threshold dose of PSC LOPs at which the point estimate attains a minimum of −2 times log-likelihood was 0 mGy. This indicated that the thresholds were not significantly >0 mGy for PSC LOPs.

DISCUSSION

In the present study, we examined the eye lens opacity for ~500 subjects from the HNBR and the nearby control area, and found that the prevalence of cortical and PSC LOPs were increased in the HNBR area, with OR at 100 mGy of 1.26 (95% CI 1.00–1.60, $P = 0.048$) and 1.73 (95% CI 1.05–2.85, $P = 0.032$) for cortical and PSC LOPs, respectively. For cortical LOPs, logistic analysis with a threshold gave a threshold point estimate of 140 mGy (90% CI 110–160 mGy). For PSC LOPs, no statistically significant threshold was obtained.

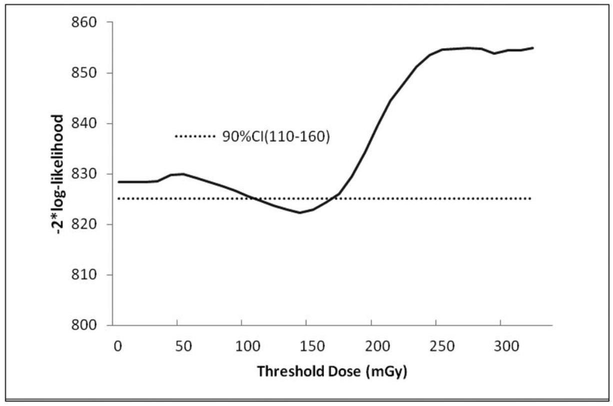

Fig. 1. Cortical LOPs −2 times log-likelihood vs threshold dose. Solid line shows the −2 times log-likelihood curve and the horizontal dashed line indicates the upper 10% point of the chi-square distribution with one degree of freedom, X2(1)(90) = 2.71, to show the 90% CI band of the threshold dose of cortical LOPs. For PSC LOPs, no threshold existed, so no confidence band is shown.

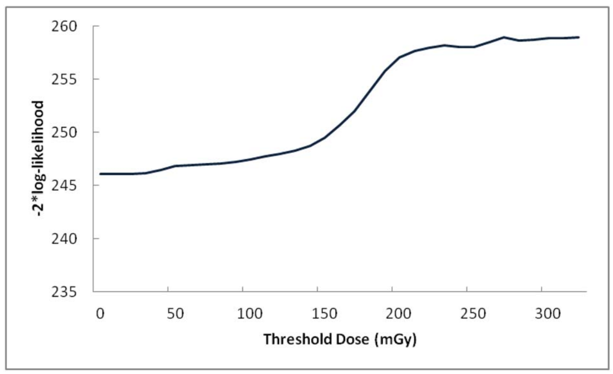

Fig. 2. PSC LOPs −2 times log-likelihood vs threshold dose. Solid line shows the −2 times log-likelihood curves and horizontal dashed lines indicate the upper 10% point of the chi-square distribution with one degree of freedom, X2(1)(90) = 2.71, to show the 90% confidence band of the threshold dose of cortical LOPs. For PSC LOPs, no threshold existed, so no confidence band is shown.

The association of PSC LOPs or cataracts with radiation exposure has been reported by several studies on acute radiation exposure or chronic exposure. A study of atomic bomb survivors by Neriishi *et al.* [5] reported that a statistically significant dose–response increase in the prevalence of postoperative cataracts, OR of 1.39 with 95% CI 1.24–1.55 at 1 Gy. Nakashima *et al.* [4] reported another atomic bomb study, with re-diagnosis by a single ophthalmologist, with a DS02 dosimetry system. The study indicated that cortical cataract showed a significant dose effect ($P < 0.002$) with an OR/Sv of 1.30 (95% CI 1.10–1.53), PSC LOPs showed a significant dose effect ($P < 0.001$), with an OR/Sv of 1.44 at age of exposure of 10 years (95% CI 1.19–1.73). Among Chernobyl liquidators, the OR at 1 Gy for PSC LOPs with stage 1+ was estimated to be 1.42 (95% CI 1.01–2.00) [6]. For chronic exposure, Little *et al*. [7] suggested that there was excess risk for cataract associated with radiation exposure for US radiologic technologists (an excess hazard ratio/mGy of 0.69×10^{-3} (95% CI 0.27×10^{-3} to 1.16×10^{-3}, $P < 0.001$). A French multicenter observational study of interventional cardiologists reported by Jacob *et al.* [25] obtained a significantly increased prevalence of PSC LOPs with OR = 3.9, 95% CI 1.3–11.4. In the Jacob study, no radiation dose was presented. Another French study reported a cumulative eye lens dose of 423 mSv (SD: 359 mSv) on average for interventional cardiologists [26]. Due to the small sample size in the current study, the CIs were very wide, so risks were probably statistically compatible with those in the other studies, even if the central estimates are much higher. In addition, the age to start the exposure may be one of factors that caused the relatively large OR estimates for PSC and cortical LOPs obtained in the present study, because most of the people have been living in the HNBR and received the radiation since their birth (only 17 people were not born in the HBRA). A meta-analysis conducted by Elmaraezy *et al.* [27] found that the frequency of posterior LOPs among interventional cardiologists was significantly higher than that among the control group (RR = 3.21; 95% CI 2.14, 4.83; $P < 0.001$) and no exposure dose was available. The crude RR = (23/479)/(6/462) = 3.70 for PSC LOPs in the present study was similar to Elmaraezy's meta-analysis.

In the present study, no statistically significant association was found for nuclear LOPs. That is also the case for the atomic bomb survivors study [4], Chernobyl liquidator study [6] and French interventional cardiologist study [25]. In the HNBR and control area, nuclear LOPs were found among 245 cases (51.1%) and 206 cases (51.2%), respectively.

Although Little *et al.* [28] reviewed the methodological problems in threshold analysis, and considered that all likelihood-based *P*-values and CIs may be incorrect, as no other generally accepted method is currently available to find the threshold dose for radiation exposure, we followed the methodology used in the atomic bomb survivor study. The existence of a dose threshold for radiation-induced cataractogenesis has long been assumed, but the available studies suggest that this cannot currently be considered as established. A recent study of atomic bomb survivors found threshold doses of 0.7 Gy (90% CI < 0–2.8) for PSC cataract, 0.6 Gy (90% CI < 0–1.2) for cortical cataract [4] and 0.1 Gy (90% CI < 0–0.8) for postoperative cataracts [5]. In the Chernobyl liquidator workers study, the dose threshold for stage 1 LOPs and stage 1 PSC LOPs were 0.34 Gy (95% CI 0.19–0.68 Gy) and 0.35 Gy (95% CI 0.19–0.66 Gy) [6], respectively, which are much higher than the estimates from the present study (140 mGy for cortical LOPs and no significant threshold for PSC LOPs). The reasons for these inconsistencies are not clear, but there are a few possible explanations for the threshold differences between the current study and others. The subjects in the other studies were under acute radiation exposure, while our study was of chronic and natural HNBR area exposure. Another factor is that age at the start of exposure is different; the subjects in our study were exposed from birth.

Information collected concerning health status came from the residents' memories, and one cannot completely eliminate the possibility that some information was not completely accurate and suffered information bias. Information on smoking and drinking lacked detail. These confounding factors might underestimate or overestimate the risk of LOPs in the present study. Another drawback of this study is that the environmental dose measurements were conducted only in about one-third of houses in each of the hamlets >20 years ago [20]. In the past, building materials were soils from local areas, so the indoor radiation dose from natural sources including thorium was higher than in the control area. With economic development, the condition of local housing has been greatly improved, and new building materials mainly from other areas were introduced into the local area and extensively used, which might narrow the difference in radiation dose between the HNBR and control areas, resulting in underestimating the risk in this study. Nonetheless, the prevalence of cortical and PSC LOPs are clearly elevated in the Yangjiang HNBR area. The present work confirmed the results obtained with previous studies [18, 19], and the ORs are similar and consistent among the three studies conducted in the 1970s [18], 2000s [19] and 2010s. The fact that 48 persons with a history of cataract surgery were deleted in the present study, requires further investigation, which may influence the results.

The results indicated population exposed to low-dose-rate radiation was at an elevated risk of cortical and PSC LOPs. A statistically significant threshold was obtained for cortical LOPs, and no threshold dose for PSC LOPS.

CONFLICT OF INTEREST

None declared.

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