

# Exposure to Atomic Bomb Radiation and Age-Related Macular Degeneration in Later Life: The Hiroshima-Nagasaki Atomic Bomb Survivor Study

Katsumasa Itakura,<sup>1,2</sup> Ikuno Takahashi,<sup>3</sup> Eiji Nakashima,<sup>4</sup> Masahide Yanagi,<sup>1,2</sup> Ryo Kawasaki,<sup>1,5</sup> Kazuo Neriishi,<sup>3,6</sup> Jie Jin Wang,<sup>1,7</sup> Tien Yin Wong,<sup>1,8</sup> Ayumi Hida,<sup>9</sup> Waka Ohishi,<sup>3</sup> and Yoshiaki Kiuchi<sup>2</sup>

<sup>1</sup>Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, University of Melbourne, Melbourne, Victoria, Australia

<sup>2</sup>Department of Ophthalmology and Visual Science, Hiroshima University, Hiroshima, Japan

<sup>3</sup>Department of Clinical Studies, Radiation Effects Research Foundation, Hiroshima, Japan

<sup>4</sup>Department of Statistics, Radiation Effects Research Foundation, Hiroshima, Japan

<sup>5</sup>Department of Public Health, Yamagata University Faculty of Medicine, Yamagata, Japan

<sup>6</sup>Yachiyo Hospital, Hiroshima, Japan

<sup>7</sup>Centre for Vision Research, Westmead Millennium Institute, University of Sydney, Sydney, New South Wales, Australia

<sup>8</sup>Singapore Eye Research Institute, Singapore National Eye Center, Duke-NUS Graduate Medical School, National University of Singapore, Singapore

<sup>9</sup>Department of Clinical Studies, Radiation Effects Research Foundation, Nagasaki, Japan

Correspondence: Yoshiaki Kiuchi, Hiroshima University, Department of Ophthalmology and Visual Sciences, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8551, Japan; ykiuchi@hiroshima-u.ac.jp.

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**PURPOSE.** To investigate the association between radiation exposure from the atomic bombings and the prevalence of age-related macular degeneration (AMD) among older residents of Hiroshima and Nagasaki.

**METHODS.** The Adult Health Study is a cohort study of atomic bomb survivors living in Hiroshima and Nagasaki, comprising 2153 participants who underwent examinations with retinal fundus photographs in 2006–2008. The radiation dose to the eye for the analysis was estimated with the revised dosimetry system (DS02). The retinal photographs were graded according to the Wisconsin Age-Related Maculopathy Grading System modified for nonstereoscopic retinal images. Early and late AMD were defined according to the type of lesion detected in the worse eye of the participants. Person-specific data were analyzed by using a logistic regression model to assess the association between radiation dose and AMD.

**RESULTS.** Among the 1824 subjects with gradable retinal images (84.7% of the overall participants), the estimated eye dose was widely distributed, with a mean of 0.45 Gy and standard deviation of 0.74 Gy. The prevalence of early and late AMD was 10.5% and 0.3%, respectively. There were no significant associations between radiation dose and AMD, with each 1-Gy increase in exposure, adjusted odds ratio was 0.93 (95% confidence interval [CI], 0.75–1.15) for early AMD and 0.79 (95% CI, 0.21–2.94) for late AMD.

**CONCLUSIONS.** No significant associations were found between atomic bomb irradiation early in life and the prevalence of early or late AMD later in life among Japanese atomic bomb survivors.

**Keywords:** age-related macular degeneration, epidemiology, radiation damage, atomic bomb, retina

Age-related macular degeneration (AMD) is a multifactorial disease, whose major risk factors include aging, cigarette smoking, and hypertension.<sup>1–3</sup> There is substantial evidence that vascular diseases, including endothelial dysfunction, and decreased levels of choroidal circulatory parameters, play a role in the pathogenesis of AMD.<sup>4–7</sup>

Ionizing radiation inhibits the growth of vascular endothelial cells (i.e., direct damage).<sup>8</sup> Radiation-induced oxidative stress induces various vascular abnormalities, including reductions in the choroidal circulation<sup>9</sup> and ischemia of the retina.<sup>10</sup> Oxidative stress spreads from targeted cells to nontargeted bystander cells<sup>11</sup> and persists months after the initial exposure (i.e., indirect damage)<sup>12</sup>; therefore, chronic oxidative stress

contributes to tissue injury later in life and the onset of pathologic conditions, such as vascular disease.<sup>13,14</sup>

The Adult Health Study (AHS), a cohort study of atomic bomb survivors of Hiroshima and Nagasaki in Japan, demonstrated a significant association between radiation exposure and retinal arteriosclerosis 55 years after exposure.<sup>15</sup> Epidemiologic evidence for the associations between exposure to low-ionizing radiation and late-occurring cardiovascular disease has been demonstrated.<sup>16</sup> Since vascular diseases and a decreased choroidal circulation can affect AMD, it is possible that the risk of AMD is increased in atomic bomb survivors, resulting from the onset of arteriosclerosis of the retina and choroid. Nevertheless, the chronic effects of ionizing radiation exposure on the development of AMD have not been investigated to date.

We aim to assess the association between past radiation exposure early in life and the presence of AMD late in life among atomic bomb survivors in the AHS population.

## METHODS

### Subjects

The Radiation Effect Research Foundation (RERF) established the Life Span Study (LSS) cohort of 120,321 survivors of the atomic bombings of Hiroshima and Nagasaki, Japan. In 1958, a series of comprehensive physical examinations was performed biennially among the AHS cohort consisting of 19,961 LSS subjects. In 1977, a total of 5000 individuals who were not within the limits of these cities at the time of the bombings were no longer followed up, and 2436 subjects were instead newly included into the AHS population. Among these 17,397 persons, 11,671 deaths occurred by the end of 2008. The surviving subjects were completely followed up with respect to death, and approximately 70% of this group who lived in areas accessible from the RERF facilities continued to participate in each examination cycle. During the period of 2006–2008, a total of 2799 subjects were randomly selected from among the AHS population, and 2153 individuals (76.9%) agreed to take part in the survey to assess the prevalence of AMD (Fig.). Of these subjects, 329 had ungradable retinal images owing to the presence of ocular media opacity (i.e., cataracts and corneal opacity) and/or poor camera focus, and 1824 participants were included in analyses of this report. The retinal images used for this report were collected during the examinations conducted in 2006–2008, after approval by the RERF Ethics Committee in line with the provisions of the Declaration of Helsinki, and written informed consent was obtained from each participant.

### Radiation Dosimetry and Other Characteristics

Individual eye dose was estimated with a revised dosimetry system (DS02) that takes into account biases arising from measurement error and the subject's physical location and shielding conditions at the time of the bombings.<sup>17</sup> For all analyses, a weighted absorbed eye dose was used in units of gray (Gy), in which the dose for an individual corresponds to the total exposure in  $\gamma$  rays + 10  $\times$  the smaller neutron dose.<sup>18</sup>

Other characteristics and potential confounders included sex, city (Hiroshima or Nagasaki), age at the time of the examination, smoking history, systolic/diastolic blood pressure, hypertension, high sensitivity C-reactive protein (hs-CRP), white blood cell (WBC) count, diabetes, body mass index (BMI), nonfasting total cholesterol (T-chol), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. The smoking status was defined as never, past, or current. The hs-CRP levels were determined by using a chemiluminescent ELISA (Nissui, Tokyo, Japan). All measurements were collected according to an automated procedure (Hitachi 7170S; Hitachi Ltd, Tokyo, Japan) under internal/external quality control. The T-chol, LDL-C, and HDL-C levels were monitored in accordance with the College of American Pathologists (Northfield, IL, USA). BMI was defined as the weight divided by the height squared ( $\text{kg}/\text{m}^2$ ).

Diabetes was diagnosed according to the American Diabetes Association criteria, which includes a nonfasting plasma glucose level of  $\geq 200$  mg/dL (7.0 mmol/L), hemoglobin A1c level of  $\geq 6.5\%$ , the use of medications for diabetes, and/or a history of diabetic retinopathy.<sup>19</sup> Hypercholesterolemia was defined as either fasting or nonfasting total cholesterol levels of  $\geq 220$  mg/dL and/or the use of relevant medication, and hypertension was defined as high blood pressure (a systolic/

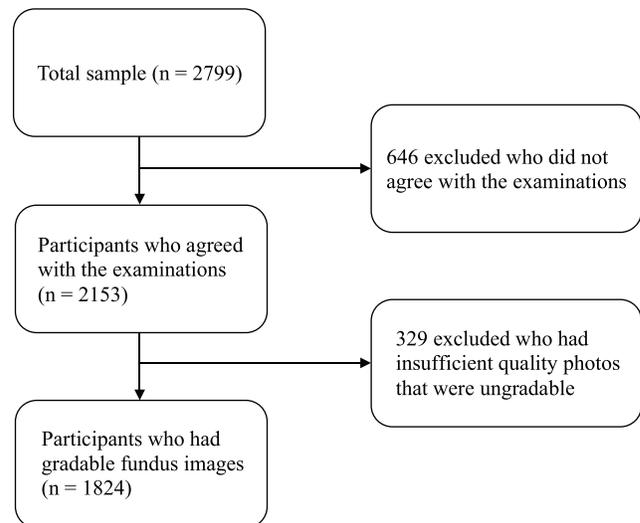


FIGURE. Data sample exclusion.

diastolic blood pressure of  $\geq 140/90$  mm Hg and/or the use of hypertensive agents).

### Assessment of AMD

All participants underwent bilateral fundus photography without pharmacologic pupil dilation, centered on the halfway point of the optic disc and macula at a  $45^\circ$  angle, using a nonmydriatic digital camera (TRC-NW200; Topcon, Tokyo, Japan). The retinal images were assessed by an ophthalmologist who was masked to the participants' characteristics, including radiation dose, using a simplified protocol for evaluating nonstereoscopic retinal images following the Wisconsin Age-Related Maculopathy Grading System,<sup>20</sup> modified for the Blue Mountains Eye Study.<sup>21</sup> A transparent plastic sheet provided by the Centre for Eye Research Australia was used for grading. A grid was printed on the plastic consisting of three circles concentric with the center of the macula (i.e., inner, middle, and outer circles corresponding to sizes of 1000, 3000, and 6000  $\mu\text{m}$  in diameter) and four radial lines in order to define subfields in the macula. A set of grading circles was also printed on the sheet, corresponding to sizes of 63, 125, 250, 350, and 650  $\mu\text{m}$  in diameter and used to estimate the size of and the area involved by drusen and/or retinal pigmentary abnormalities. The plastic sheet was placed on the computer monitor, and AMD lesions appearing within the grid of the macula were measured. The number of drusen was counted and the sharpness was examined. The size and area of drusen were determined by using the grading circles on the sheet that were adjusted to the magnification of retinal images on the monitor according to the width of the major branch retinal vein crossing the optic disc margin, measuring approximately 125  $\mu\text{m}$ . Patients with retinal images showing confounding lesions in the macula (e.g., epiretinal membrane, branch/central retinal vein occlusion, diabetic retinopathy with macular edema or myopic retinopathy) and/or a lack of detailed grading of the AMD lesions due to the presence of confounding lesions were considered to not have AMD.

### Definition of AMD

Age-related macular degeneration was classified into two categories, early or late, according to the severity. Early AMD was defined as the presence of either "soft indistinct or reticular drusen" or "both soft distinct drusen and retinal pigment

TABLE 1. Characteristics by DS02 Estimated Radiation Exposed Dose, the Hiroshima-Nagasaki Atomic Bomb Survivor Study

	DS02 Estimated Exposed Dose, Gy					P Value for Homogeneity Test*	P Value for Trend Test, Age, Sex Adjusted
	<0.005	0.005 to <0.5	0.5 to <1	1 to <2	≥2		
No. of subjects, <i>n</i> (%)	796	491	235	215	87		
Men	294 (36.9)	178 (36.3)	84 (35.7)	85 (39.5)	41 (47.1)	0.336	
Current smokers	82 (10.3)	50 (10.2)	27 (11.5)	24 (11.2)	6 (6.9)	0.157	0.259
Diabetes	194 (24.4)	130 (26.5)	58 (24.7)	57 (26.5)	34 (39.1)	0.069†	0.009
Hypertension	478 (60.1)	301 (61.3)	147 (62.6)	119 (55.4)	51 (58.6)	0.559†	0.657
Hypercholesterolemia	437 (55.0)	299 (61.3)	139 (59.2)	99 (46.5)	42 (48.8)	0.003†	0.045
Distribution of factors‡							
CRP, µg/L	0.20 (0–14.75)	0.17 (0.003–6.40)	0.17 (0.007–2.56)	0.25 (0.002–7.21)	0.24 (0.012–3.29)	0.011	0.144
WBC, ×10 <sup>2</sup> /mm	55.4 ± 15.1	55.8 ± 16.3	56.5 ± 15.3	56.5 ± 16.1	58.8 ± 21.0	0.748	0.072
BMI, kg/m <sup>2</sup>	23.0 ± 3.4	23.1 ± 3.3	22.9 ± 3.0	22.4 ± 3.7	22.1 ± 3.5	0.002	<0.0001
Age, y	74.7 ± 6.6	73.6 ± 6.9	75.0 ± 6.4	73.9 ± 6.6	73.0 ± 7.2	0.003	
No. of AMD, <i>n</i> (%)	80 (10.1)	59 (12.0)	24 (10.2)	29 (13.5)	5 (5.7)	0.267†	0.438
Early AMD	79 (9.9)	56 (11.4)	22 (9.4)	29 (13.5)	5 (5.7)	0.280†	0.471
Late AMD	1 (0.13)	3 (0.61)	2 (0.85)	0 (0)	0 (0)	0.249†	0.728
Neovascular	0 (0)	2 (0.41)	1 (0.43)	0 (0)	0 (0)	0.280†	0.697
Geographic atrophy	1 (0.13)	1 (0.20)	1 (0.43)	0 (0)	0 (0)	0.751†	0.995
No. of soft drusen, <i>n</i> (%)							
Distinct	75 (9.4)	47 (9.7)	16 (6.8)	9 (4.2)	8 (9.1)	0.079†	0.248
<10	44 (5.6)	34 (7.0)	10 (4.3)	6 (2.8)	5 (5.7)	0.205†	0.284
≥10	35 (4.4)	16 (3.3)	8 (3.4)	3 (1.4)	2 (2.3)	0.292†	0.095
Indistinct	77 (9.7)	56 (11.5)	23 (9.8)	29 (13.6)	5 (5.7)	0.256†	0.514
<10	42 (5.3)	32 (6.6)	12 (5.1)	15 (7.0)	4 (4.6)	0.765†	0.724
≥10	36 (4.5)	31 (6.4)	11 (4.7)	15 (7.0)	1 (1.1)	0.153†	0.457
Maximum size < 125 µm	116 (14.6)	87 (17.9)	29 (12.4)	25 (11.7)	10 (11.5)	0.139†	0.048
125 to <250 µm	32 (4.0)	17 (3.5)	9 (3.8)	11 (5.1)	2 (2.3)	0.659†	0.794
≥250 µm	2 (0.25)	1 (0.20)	0 (0)	2 (0.9)	1 (1.1)	0.163†	0.099
No. of pigmentation, <i>n</i> (%)							
Hyperpigmentation	1 (0.13)	0 (0)	1 (0.43)	0 (0)	0 (0)	0.575†	0.833
Hypopigmentation	5 (0.63)	0 (0)	1 (0.43)	0 (0)	0 (0)	0.342†	0.296

\* Two-sided *P* value for  $\chi^2$  test and Kruskal-Wallis rank test for continuous variables.

† *P* value for Fisher's exact test.

‡ Continuous variables are presented as the average ± standard deviation, except for CRP, which is shown as the range.

epithelium (RPE) abnormalities." The type of drusen was classified by the size and sharpness of the edges; a hard druse was defined as that measuring less than 63 µm in diameter, while a soft druse was defined if it was more than 63 µm in diameter. Soft drusen were classified into distinct and indistinct types. We also measured the maximum soft drusen size, defined as the largest size of soft drusen within the grid of the macula. Retinal pigmentary abnormalities were graded as hypopigmentation or hyperpigmentation. Late AMD was defined as either neovascular AMD or geographic atrophy. Neovascular AMD lesions were defined as lesions exhibiting serous or hemorrhagic detachment of the RPE or sensory retina, subretinal or sub-RPE hemorrhage, or subretinal fibrous scar tissue. Geographic atrophy was defined as the presence of visible choroidal vessels containing discrete atrophic areas with a sharp border measuring 175 µm in diameter or greater. Intra-grader agreement was assessed by using the  $\kappa$  statistic among 50 eyes in randomly selected subjects and was excellent regarding the presence of early and late AMD ( $\kappa = 0.83$ ).

## Data Analysis

A weighted absorbed eye dose, individually estimated, was used for analysis. The participants were classified according to

the status of the worse eye, based on the disease severity (i.e., patients with early AMD in one eye and late AMD in the other eye, were classified as having late AMD). All analyses were conducted by using the Stata 11 software program (Stata Corp., College Station, TX, USA). The  $\chi^2$  test and Fisher's exact test were used to compare the demographic characteristics according to the dose categories. Age and sex-adjusted comparisons for continuous variables (i.e., CRP, WBC, and BMD) across the dose groups were performed by using linear regression analyses. Multivariable-adjusted logistic regression models were used to assess the associations between prevalence of AMD or AMD lesions and radiation dose after adjusting for age, sex, smoking, and city (model A), and further adjusted for diabetes, hypertension, hypercholesterolemia, WBC count, and BMI (model B). Odds ratios (ORs) of presenting signs of early and late AMD associated with each 1-Gy increase in the exposure were presented. Because age and sex were distributed differently across the dose strata, trends across the dose groups were tested after adjustment for these variables. All 95% confidence intervals (CIs) were calculated from the Wald statistic, and *P* values for significance were determined according to the two-sided Wald tests in which a *P* value less than 0.05 was considered to be significant.

**TABLE 2.** Crude Associations of AMD in the Hiroshima-Nagasaki Atomic Bomb Survivor Study Population

	OR	95% CI
Sex, women vs. men	0.84	0.62-1.13
Age, per 10 y	1.30	1.04-1.62
Radiation dose, per 1 Gy	0.92	0.75-1.14
Smoking, current vs. no smoker*	1.18	0.87-1.59
Past smokers vs. never	1.20	0.69-1.82
Current smokers vs. never	1.12	0.86-1.67
Diabetes	1.25	0.91-1.73
Hypertension	1.06	0.79-1.44
Hypercholesterolemia	0.89	0.66-1.19
CRP, per 1 µg/L	1.11	0.90-1.37
WBC, per 10 <sup>2</sup> /mm <sup>3</sup>	1.00	0.99-1.01
BMI, per 1 kg/m <sup>2</sup>	0.99	0.95-1.04

\* No smoker group consists of never and past smokers.

## RESULTS

The number of cases of AMD and its related signs, by radiation dose in the eye, are shown in Table 1. The mean age at the time of the examination among the participants with gradable photographs ( $n = 1824$ ) was  $73.8 \pm 6.7$  years, with a range of 61 to 97 years. Among the 1824 subjects, 43.6% were exposed to less than 0.005 Gy, and 4.8% were exposed to more than 2 Gy. There were 197 AMD patients, including 81 males and 116 females. The prevalence of early and late AMD was 10.5% and 0.33%, respectively. Among the cases of late AMD, both neovascular AMD and geographic atrophy were found in three participants (0.16%). The prevalence of small soft drusen (maximum diameter  $< 125$  µm) was 14.6%, while the prevalence of large drusen (maximum diameter  $\geq 125$  µm) was 4.2%. Meanwhile, pigmentary abnormalities were present in 0.38% of the patients, increased retinal pigment was noted in 0.11%, and RPE depigmentation was detected in 0.33%. Confounding lesions in the macula, such as lesions in the epiretinal membrane and diabetic retinopathy, were observed in 38 eyes (2.08%). Whereas the prevalence of AMD and distribution of AMD lesions did not show any radiation-related trends, the prevalence of small soft drusen tended to decrease in association with an increasing dose of radiation exposure ( $P$  for trend = 0.048).

Table 2 shows the results of the univariate analysis of the associations between single potential covariates and the prevalence of any AMD. The prevalence of AMD was associated with age (OR per 10 years of age, 1.30; 95% CI, 1.04-1.62), but not the other factors or dose of exposure.

There were no statistically significant associations between the prevalence of early AMD, late AMD, or both, and the dose of radiation; adjusted OR per 1-Gy increase in exposure (model A) was 0.93 (95% CI, 0.75-1.15), 0.79 (95% CI, 0.21-2.94), and 0.92 (95% CI, 0.75-1.14), respectively (Table 3). The adjusted ORs for model B were similar. No threshold effect was indicated.

The prevalence of small drusen ( $< 125$  µm in diameter) tended to decrease in association with an increasing dose of radiation (adjusted OR, 0.82; 95% CI, 0.67-1.00; model A). This trend was not found to be statistically significant in model B.

## DISCUSSION

Past reports of neovascular AMD patients who received radiation treatment, ranging from 7.5 to 24 Gy in multiple treatments, have demonstrated no significant visual improvements despite the fact that the radiation stabilized and/or suppressed choroidal neovascularization.<sup>22,23</sup> This observation

**TABLE 3.** Adjusted Associations Between Exposed Radiation Dose and Presence of AMD or AMD Lesions in the Hiroshima-Nagasaki Atomic Bomb Survivor Study Population

	Model A*		Model B*	
	OR, per Gy	95% CI	OR, per Gy	95% CI
<b>AMD prevalence</b>				
Early AMD	0.93	0.75-1.15	0.92	0.74-1.14
Late AMD	0.79	0.21-2.94	0.85	0.24-2.98
Any AMD	0.92	0.75-1.14	0.92	0.74-1.13
<b>AMD-related manifestations</b>				
Soft distinct drusen	0.82	0.63-1.06	0.83	0.64-1.08
Soft indistinct drusen	0.93	0.76-1.15	0.93	0.75-1.15
<b>Maximum soft drusen size, µm</b>				
<125	0.82	0.67-1.00	0.83	0.68-1.01
125-250	1.02	0.74-1.40	1.02	0.74-1.41
$\geq 250$	1.90	0.95-3.77	1.75	0.85-3.57
Any pigmentary abnormalities	0.46	0.08-2.61	0.41	0.08-2.22

\* Model A is adjusted for city, sex, age, and smoking; model B is adjusted for city, sex, age, smoking, diabetes, hypertension, hypercholesterolemia, WBC count, and BMI.

suggests that eye irradiation has an adverse impact on the retinal function,<sup>22</sup> even in patients without pathologic findings in the retina or optic nerve (according to an observational survey conducted for 24 months after radiotherapy).<sup>24</sup> A substantial increase in the risk of mortality as well as morbidity and stroke among Japanese atomic bomb survivors<sup>25</sup> also raises potential concerns regarding the risk of AMD in these survivors, as AMD and stroke are thought to share common cardiovascular mechanisms.<sup>26-29</sup>

Our study of Japanese atomic bomb survivors provided a unique opportunity to examine the late effects of radiation on the development of AMD by using the modified scale of the Wisconsin Age-Related Maculopathy Grading System, a previously validated method.<sup>21,30-38</sup> Consequently, the results showed that the dose of radiation exposure was not significantly associated with the prevalence of AMD. With a background rate of AMD of 10%, variance inflation factor of 10%, a study power of 90%, and significance level of 5%, our study should be able to detect the smallest OR of 1.3 for each 1-Gy increase in exposure. We cannot exclude the possibility that a weaker association (OR smaller than 1.3) may exist.

Long-lasting oxidative stress following radiation exposure<sup>39</sup> may suppress neovascularization in the retina. In fact, the prevalence of neovascular AMD among our study subjects was indeed lower than that observed in the Japanese general population: 0.16% (atomic bomb survivors,  $73.8 \pm 6.7$  years of age) versus 0.67% (the Hisayama Study,<sup>36</sup>  $65.2 \pm 8.9$ ) and 0.3% (the Funagata Study,<sup>35</sup>  $59.4 \pm 11.3$ ). Alternatively, the survival bias of our cohort sample may explain the low prevalence of AMD compared to that seen in the general older population. Our data showed that the participants in the higher radiation exposure categories were younger and less likely to have late AMD (Table 1), indicating an increased mortality rate among those with high levels of exposure to radiation.

Focusing on the AMD-related findings, our results suggested a decreased OR of 1-Gy dose associated with small soft drusen ( $< 125$  µm). Further follow-up is needed to determine the effects of radiation on the incidence of early AMD lesions among atomic bomb survivors.

The current study has several limitations. First, there may be selection bias resulting from the inclusion of healthy survivors.

Although the radiation dose did not differ significantly across the groups of included and excluded participants, the distributions of other characteristics were significantly different (Supplementary Table S1). We expect that the cohort participants who died would demonstrate substantially different distributions in some of the characteristics. Second, fundus images for high-dose groups may tend to be ungradable owing to the effects of radiation-related opacity in the lens.<sup>15</sup> In fact, the rate of ungradable cases (15.3%) in this study was similar to that observed in the Funagata Study (17.1%),<sup>35</sup> although higher than that reported in other studies (0.3%~4.3%).<sup>33,34,36</sup> An assessment of this issue using a test of the likelihood of ungradable cases, however, showed no significant differences in the exposure dosages (data not shown). Third, AMD was assessed only once, and no previous retinal photographs were taken at baseline in order to assess the incidence or progression of AMD. Nevertheless, we do not expect any AMD in this cohort before exposure, when the study subjects were young adults. Therefore, any associations with AMD should be considered prospective in nature.

In conclusion, the current epidemiologic study showed no statistically significant associations between radiation exposure early in life and the prevalence of AMD in later life among Japanese atomic bomb survivors. However, the number of cases with late AMD or large soft drusen was very small in our study sample. Further follow-up and comparisons with nonexposed samples are expected to shed light on the effects of radiation on the risk of AMD and progression of AMD lesions.

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