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Glaucoma in Atomic Bomb Survivors

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Radiation has been associated with increases in noncancerous diseases. An effect of low-dose radiation on the prevalence of clinically detected glaucoma has not been previously reported. We therefore investigated the prevalence of glaucoma in A-bomb survivors and its possible association with radiation dose. A total of 1,589 people who participated in the clinical examination program for A-bomb survivors at the Radiation Effects Research Foundation (RERF) between October 2006 and September 2008 and who had reconstructed radiation doses, were recruited into this cross-sectional screening study. The prevalence of glaucoma and its dose-response relationship to A-bomb radiation were measured. Each subject underwent an initial screening consisting of an interview and ophthalmological examination. Questionable cases with any indication of ocular disease, including glaucoma, were referred to local hospitals for more comprehensive evaluation. A diagnosis of glaucoma was made based on specific optic disc appearance, perimetric results and other ocular findings. Of 1,589 eligible people, we detected 284 (17.9%) cases of glaucoma overall, including 36 (2.3%) cases of primary open-angle glaucoma with intraocular pressure levels greater than 21 mmHg, 226 (14.2%) cases of normal-tension glaucoma and 25 (1.6%) cases of primary angle-closure glaucoma. Seven glaucoma risk factors were examined as potential confounders but only two needed to be included in the final model. Binary regression using a generalized estimating equation method, with adjustment for gender, age, city, cataract surgery or diabetes mellitus, revealed an odds ratio at 1 Gy of 1.31 (95% confidence interval 1.11–1.53, $P = 0.001$) in the case of normal-tension glaucoma, but no association for other types of glaucoma. The prevalence of normal-tension glaucoma may increase with A-bomb radiation dose, but uncertainties associated with nonparticipation (59% participation) suggest caution in the interpretation of these results until they are confirmed by other studies.

INTRODUCTION

Glaucoma, a major cause of blindness worldwide, shows characteristic changes in the optic nerve head and visual fields (*1*). Progressive degeneration of retinal ganglion accompany those changes and leads to blindness. Glaucoma is associated with many risk factors including: increased intraocular pressure; family history; aging; vascular factors that alter ocular blood flow like arteriosclerosis; elevated systemic blood pressure; vasospasms and corneal thickening (*2, 3*). The Tajimi study, a major population based epidemiologic study of glaucoma in Japan (*11, 12*), reported a prevalence of glaucoma of 5.8% in males and 6.7% in females at ages 60–69 and 10.6% in males and 10.5% in females at ages 70–79 (*12*).

As a complication of high radiotherapy doses to the eye, neovascular glaucoma has been found in 7–11% of patients (*4–7*). Doses of radiation more than about 10 Gy obstruct the microcirculation due to plaque formation that reduces ocular blood flow in the eye and leads to neovascularization in the iris or angle that results in high intraocular pressure. However, relatively low doses of radiation have not shown excess ocular hypertension in radiation workers in the few available studies (*8, 9*). Yamada *et al*. reported that the incidence of glaucoma significantly decreases with increasing A-bomb radiation doses (*10*), but the diagnoses in that study were based on medical history alone and not on ocular reexaminations, so that there may have been many false negatives. For instance, in the Tajimi study, 90% of subjects diagnosed with glaucoma by systematic screening and evaluation had no prior diagnosis of glaucoma. (*11*).

To further elucidate the effects of low doses of radiation, we investigated the prevalence of glaucoma in A-bomb

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2699 Adult Health Study participants in biennial health examination during 2006. 10 – 2008.9

↓ 746 (28%) did not agree to undertake screening examination

1953 (72%) participated in screening examination

↓ 915 (34%) were found to be normal in screening examination

1038 (38%) were referred for detailed examinations

↓ 355 (13%) did not agree to undertake detail examinations

↓ 378 (14%) were found not to have glaucoma nor ocular hypertension in the detailed examination

305 (11%) were diagnosed as having glaucoma or ocular hypertension

↓ 9 (.3%) were excluded because information on diabetes mellitus was not available.

1589 were included in the analysis (59% of the 2699 AHS participants)

FIG. 1. Number of subjects.

survivors based on comprehensive ophthalmologic examinations and conducted a dose-response analysis. The examinations were performed during 2006–2008, 51–53 years after the A-bomb radiation exposure.

STUDY SUBJECTS AND METHODS

This study was conducted as part of the Adult Health Study (AHS) of A-bomb survivors at the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki and was approved by the RERF Human Investigation Committee (IRB). The AHS, originally consisting of about 17,000 participants matched across the radiation-dose range on gender and age, has been conducting biennial health examinations since 1958 (*13*). Among 2,699 AHS attendees between October 2006 and September 2008 with known radiation doses, 1,953 people (72%) agreed to participate in the visual examination study (Fig. 1). Among the participants, 1,038 people were suspected to have an abnormality and were requested to undergo a detailed examination at Hiroshima or Nagasaki University hospitals. However, 355 (34%) did not undergo the detailed examination and 9 whose information on diabetes mellitus was not available were excluded. The analysis include 1,589, 59% of the 2,699 AHS participants (Fig. 1). Information on a number of the potential confounding factors, such as education, smoking, hypertension and obesity, were obtained from the AHS database.

Screening Examination at RERF

After providing informed consent, participants were asked to complete questionnaires for their glaucoma-related medical history. Examiners were not aware of the radiation doses of study subjects. Refraction and intraocular pressure (IOP) was measured three times with a noncontact

TABLE 1
Medication for Glaucoma and Participation in the Glaucoma Study by Radiation Dose Group [No. Medication Cases/Total No. in Group and (%)]

Study status	Dose (mGy)					Total
	<5	5 – <200	200 – <1,000	1,000 – <2,000	> = 2,000	
All potential examinees	80/1,168 (6.8)	37/385 (9.6)	52/676 (7.7)	14/331 (4.2)	12/139 (8.6)	195/2699 (7.2)
Screening nonparticipants	29/296 (8.9)	16/120 (13.3)	17/205 (8.3)	6/87 (6.9)	4/38 (10.5)	72/746 (9.7)
Referral nonparticipants	25/147 (17.0)	15/49 (30.6)	24/99 (24.2)	5/35 (14.3)	7/25 (28.0)	76/355 (21.4)
Odds ratio for nonparticipants, 1.00, $P = 0.98^a$						
Participants	26/725 (3.6)	6/216 (2.8)	11/372 (3.0)	3/209 (1.4)	1/76 (1.3)	47/1598[b] (2.9)
Odds ratio for participants, 0.63, $P = 0.09^a$						
Comparison of dose response slopes between nonparticipants and participants, $P < 0.001$						

[a] Odds ratio at 1 Gy based on a dose-response analysis.
[b] Among 1,598 participants, 9 people whose information on diabetes was not available were excluded from further analyses.

TABLE 2
Numbers (%) of Glaucoma Cases at Examination by Age and Gender

Diagnosis	Age –69	70–79	80–	Total
	Males (average age = 73.4)			
	(N = 199)	(N = 309)	(N = 81)	(N = 589)
Primary open-angle glaucoma	32 (16.1)	60 (19.4)	20 (24.7)	112 (19.0)
IOP > 21 mmHg	5 (2.5)	11 (3.6)	2 (2.5)	18 (3.1)
IOP ≤ 21 mmHg (normal-tension glaucoma)	27 (13.6)	49 (15.9)	18 (22.2)	94 (16.0)
Primary angle-closure glaucoma	2 (1.0)	3 (1.0)	1 (1.2)	6 (1.0)
Secondary glaucoma	2 (1.0)	1 (0.3)	1 (1.2)	4 (0.7)
Other glaucoma	1 (0.5)	0 (0)	0 (0)	1 (0.2)
All cases of glaucoma[a]	34 (17.0)	60 (19.4)	21 (25.9)	115 (19.5)
Ocular hypertension	3 (1.5)	6 (1.9)	2 (2.5)	11 (0.9)
	Females (average age = 74.9)			
	(N = 283)	(N = 466)	(N = 251)	(N = 1000)
Primary open-angle glaucoma	25 (8.8)	71 (15.2)	54 (21.5)	150 (15.0)
IOP > 21 mmHg	1 (0.4)	10 (2.1)	7 (2.8)	18 (1.8)
IOP ≤ 21 mmHg (normal-tension glaucoma)	24 (8.5)	61 (13.1)	47 (18.7)	132 (13.2)
Primary angle-closure glaucoma	2 (0.7)	9 (1.9)	8 (3.2)	19 (1.9)
Secondary glaucoma	0 (0)	4 (0.9)	2 (0.8)	6 (0.6)
Other glaucoma	0 (0)	0 (0)	0 (0)	0 (0)
All cases of glaucoma[a]	27 (9.5)	80 (17.2)	62 (24.7)	169 (16.9)
Ocular hypertension	0 (0)	6 (1.3)	4 (1.6)	10 (1.0)
	Total (average age = 74.3)			
	(N = 482)	(N = 775)	(N = 332)	(N = 1589)
Primary open-angle glaucoma	57 (13.9)	131 (16.9)	74 (22.3)	262 (16.5)
IOP > 21 mmHg	6 (1.2)	21 (2.7)	9 (2.7)	36 (2.3)
IOP ≤ 21 mmHg (normal-tension glaucoma)	51 (10.6)	110 (14.2)	65 (19.6)	226 (14.2)
Primary angle-closure glaucoma	4 (0.8)	12 (1.5)	9 (2.7)	25 (1.6)
Secondary glaucoma	2 (0.4)	5 (0.6)	3 (0.9)	10 (0.6)
Other glaucoma	1 (0.2)	0 (0)	0 (0)	1 (0.1)
All cases of glaucoma[a]	61 (12.3)	140 (18.1)	83 (25.0)	284 (17.9)
Ocular hypertension	3 (0.5)	12 (1.5)	6 (1.8)	21 (1.3)

[a] All glaucoma counts individuals only once, even if they had glaucoma in both eyes.

tonometer (Topcon CT-90A) and the mean value was used. Digital color photographs of the fundus were obtained with the pupil undilated using a Topcon digital fundus camera (Topcon NW6S) with angles of 30 and 45 degrees. The visual field was screened using a frequency doubling technology (FDT) C-20-1 screener (Humphrey Instruments). A definitive glaucoma examination was recommended when the subject was suspected to have any ocular disease. The screening criteria for referral for a definitive examination and the criteria for glaucoma diagnosis were similar to those of the Tajimi study (*11*). The criteria to refer them for definitive examination were intraocular pressure >18 mmHg and at least one of the following: vertical cup-to-disc ratio of optic nerve head >0.6; difference between the two eyes in vertical cup-to-disc ratio of >0.2; nerve fiber layer defect or splinter hemorrhage; at least 1 abnormal test point in the FDT visual field test; or any abnormal findings in the fundus photograph.

Definitive Examination and Diagnosis

Glaucoma specialists from Hiroshima and Nagasaki University Hospitals reviewed the examination records and referred participants to those hospitals for a definitive examination when the subject was suspected to have any ocular disease. At the time of referral, informed consent was obtained concerning use of the University Hospital findings by RERF.

In the definitive examination, a slit-lamp biomicroscopic examination, applanation tonometry, a visual field test using a Humphrey Field Analyzer 30-2 SITA standard program and gonioscopy with stereoscopic disc photographs (Topcon TR 80) were performed. If a glaucomatous disc change or nerve fiber defect was found and if the hemifield-based visual field abnormality was compatible with optic disc appearance or nerve fiber defect, the eye was diagnosed as having glaucoma. When the visual field test result was unreliable or unavailable, diagnosis was made using disc

TABLE 3
Numbers of Glaucoma Cases by Radiation Dose Intervals

	Radiation dose (Gy) (Mean eye dose)					
Type of glaucoma	0 – <0.005 (0.001) (N = 721)	0.005 – <0.2 (0.097) (N = 214)	0.2 – <1 (0.561) (N = 369)	1 – <2 (1.375) (N = 209)	2 – (3.006) (N = 76)	Total (0.468 Gy) (N = 1,589)
Primary open-angle glaucoma						
IOP > 21 mmHg	17 (2.4)[a]	6 (2.8)	4 (1.1)	9 (4.3)	0 (0.0)	36 (2.3)
IOP ≤ 21 mmHg (normal-tension glaucoma)	92 (12.8)	24 (11.2)	57 (15.4)	38 (18.2)	15 (19.7)	226 (14.2)
Primary angle-closure glaucoma	12 (1.7)	5 (2.3)	6 (1.6)	2 (1.0)	0 (0.0)	25 (1.6)
Secondary glaucoma	5 (0.7)	1 (0.5)	3 (0.8)	0 (0.0)	1 (1.3)	10 (0.6)
Other glaucoma	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
All cases of glaucoma	122 (16.9)	32 (15.0)	68 (18.4)	47 (22.5)	15 (19.7)	284 (17.9)
Ocular hypertension	8 (1.1)	4 (1.9)	8 (2.2)	1 (0.5)	0 (0.0)	21 (1.3)

[a] Percentage in the dose categories.

change only. When the cup-to-disc ratio of the optic nerve head was 0.9 or more, the rim width at the superior portion (11–1 o'clock position) or the inferior portion (5–7 o'clock position) was 0.05 or less of the disc diameter or the difference of the vertical cup-to-disc ratio was 0.3 or more between the two eyes, the eye was diagnosed as having glaucoma. In cases where the optic disc showed glaucoma-like changes but the eye did not satisfy the above criteria and we could not obtain a reliable or compatible hemifield-based defect in the visual field test, the eye was diagnosed as having suspect glaucoma.

All six ophthalmologists from Hiroshima and Nagasaki Universities met periodically to decide the diagnosis of suspected cases. Consensus was reached through discussion, referring to all available data. Only definite diagnoses were included in the analyses.

We categorized the subjects into nonglaucoma, primary open-angle glaucoma (POAG, IOP > 21 mmHg), normal-tension glaucoma (POAG with IOP 21 mmHg or less), primary angle-closure glaucoma (PACG), ocular hypertension (OH) and secondary glaucoma depending on the slit lamp and gonioscopic findings. Eyes in which we could not determine the type of glaucoma were classified as ''others''.

Statistical Analysis

Radiation dose-response analyses were based on the Dosimetry System 2002 (DS02) (*14*) eye radiation dose in gray (Gy), using the same methods as in previous studies: weights of 1 for gamma and 10 for neutron doses, truncation of shielded kerma doses at 4 Gy, and doses adjusted for 35% dosimetry-estimation error (*15*).

Statistical analyses using generalized estimating equations (GEE) (*16*) were conducted to find the association between glaucoma prevalence in both eyes and explanatory variables. We denoted the prevalence of a specific type of glaucoma as p_1 for the right eye and p_2 for the left eye and assumed logistic models for these eye-specific prevalences, for $j = 1, 2$,

$$\ln\left(\frac{p_j}{1-p_j}\right) = \alpha_0 + \alpha_1 C + \alpha_2 G + \alpha_3 E + \beta D + \alpha_4 (j-1) + \alpha_5 DM + \alpha_6 Cata_j, \qquad \text{(Model 1)}$$

where C and G are city (Nagasaki vs. Hiroshima) and gender (female vs. male) indicators, $E =$ (age at examination – 75)/10, D is radiation dose to the eye treated as a continuous variable, DM is an indicator of diabetes mellitus, $Cata_j$ is an indicator of cataract surgery for the jth eye, and the α's and β are regression parameters. The common eye-specific odds ratio for a radiation exposure of 1 Gy is $\exp(\hat{\beta})$, where $\hat{\beta}$ is the estimate of dose-response parameter β. The above model was denoted as Model 1.

Model 2 included the variables in Model 1, plus additional potential confounding variables as shown in Table 4, including risk factors such as education, smoking, diabetes, hypertension and obesity. Since some variables in Model 2 had missing values, the numbers differ between models (1,589 for Model 1 and 1,483 for Model 2). The STATA statistical package was used for analyses. Two-sided P values and 95% confidence intervals were based on the Wald statistic.

RESULTS

Because of the relatively high rates of nonparticipation in the screening (28%) and referral (34%) examinations, extensive analyses were conducted for possible selection biases. This was done using a history of glaucoma medication as a health endpoint; information which was usually available in the routine AHS clinical records. Analyses were then conducted with respect to both glaucoma risk factors and glaucoma medication history to determine if glaucoma-study participants differed from nonparticipants on these factors, or if their radiation dose-response relationships differed for these factors. The main findings from the bias analyses, partly shown in Table 1, were that: (1) city (Hiroshima or Nagasaki), gender and history of diabetes

TABLE 4
Association of A-Bomb Radiation with Questionnaire Items Related to Reported Glaucoma (Odds Ratio at 1 Gy)

Items	Odds ratio	95% Confidence interval
Ophthalmologic diseases under treatment[a]		
Cataract (n = 1,762)	1.18	1.03, 1.36
Congenital cataract (n = 13)	0.75	0.33, 1.72
Glaucoma, types unspecified (n = 112)	0.70	0.49, 0.98
Retinal bleeding (n = 91)	1.31	1.04, 1.66
Retinal detachment (n = 36)	1.25	0.96, 1.62
Trauma (n = 43)	1.14	0.82, 1.59
Uveitis (n = 9)	1.46	0.84, 2.55
Toxic cataract (toxic drug induced cataract, n = 7)	–	–
After cataract[f] (n = 36)	1.50	1.04, 2.14
Instillation (use of eye drops, n = 1,510)	1.01	0.89, 1.15
Surgical history[a] for		
Cataract (n = 547)	1.28	1.09, 1.50
Glaucoma (n = 28)	0.33	0.10, 1.14
Retinal bleeding (n = 54)	1.33	1.00, 1.77
Detachment (n = 20)	1.12	0.79, 1.58
Trauma (n = 9)	–	–
Systemic diseases and treatments[b]		
Diabetes mellitus (n = 280)	1.20	1.03, 1.40
Hypertension (n = 854)	0.97	0.85, 1.11
Steroid therapy (n = 70)	0.87	0.61, 1.23
Radiotherapy of head and neck (n = 12)	1.19	0.65, 2.17
Chemotherapy (n = 67)	1.14	0.85, 1.51
Junior high (n = 489) vs. University education[c]	0.94	0.81, 1.09
High school (n = 857) vs. University education[d]	1.07	0.94, 1.22
Smoking [smoker (n = 158)]	0.96	0.78, 1.19
Underweight [underweight (n = 103)][e]	1.31	1.06, 1.63
Obese [obese (n = 559)][e]	0.84	0.73, 0.97
Glaucoma history[b] in		
Father (n = 9)	0.30	0.05, 1.78
Mother (n = 27)	0.90	0.53, 1.53
Both parents (n = 34)	0.72	0.40, 1.28
Uncle or aunt (n = 14)	1.04	0.54, 2.01
Brother or sister (n = 38)	0.86	0.52, 1.43
Son or daughter (n = 6)	1.80	0.98, 3.33

[a] Number of eyes with GEE method.
[b] Number of cases with diseases with logistic method.
[c] Referent category.
[d] Referent category.
[e] Obesity categories: underweight; BMI <18, normal; BMI =18 – <24, obese; BMI > =24, normal was the referent category.
[f] Post-surgical regrowth of epithelial cells in the lens capsule that impair vision.

mellitus or of cataract surgery showed no associations of consequence with study participation, although a larger percentage of nonparticipants, irrespective of radiation dose, had a prior history of glaucoma medication; (2) age had a strong effect on study participation, with more nonparticipation at older ages, so age clearly needed to be adjusted for in the analyses; and (3) there was no clear association between radiation dose and prevalence of glaucoma medication history in nonparticipants (odds ratio at 1 Gy of 1.00, $P = 0.98$) and participants (odds ratio 0.63, $P = 0.09$). The slopes of the two linear dose-response functions did differ ($P < 0.001$) for glaucoma medication, but the direction of the difference would not suggest that participants were biased toward glaucoma in an upward direction.

The ophthalmologic examination identified 284 people (17.9%) as having glaucoma. Table 2 shows a further breakdown of glaucoma subtypes by age and gender in the current study. Glaucoma was slightly more prevalent among males and it increased with age for both genders. Table 3 indicates the breakdown by glaucoma subtype and radiation dose. The percentages indicate an increased prevalence with dose for normal-tension glaucoma.

Table 4 examines the association of various individual glaucoma risk factors with radiation exposure. Significant associations with radiation were observed for history of cataract, glaucoma, retinal bleeding, aftercataract, cataract surgery and diabetes mellitus. It should be noted that the association of radiation with reported glaucoma was in the negative direction. Radiation did not show any association with a familial history of glaucoma.

Based on the factors in Table 4 that were statistically significant, GEE logistic regression analysis was conducted

TABLE 5
Results of Binary Regression Analysis of Glaucoma Prevalence: Odds Ratios for Radiation at 1 Gy with Adjustment for Gender, Age, City, Cataract Surgery and Diabetes Mellitus

Diagnosis	N	Odds ratio (95%CI)	*P*
Primary open-angle glaucoma			
IOP > 21 mmHg	36 (58)[a]	0.79 (0.52, 1.21)	0.28
IOP ≤ 21 mmHg (normal-tension glaucoma)	226 (417)	1.31 (1.11, 1.54)	0.001
Primary angle-closure glaucoma	25 (47)	0.54 (0.29, 1.02)	0.06
Secondary glaucoma	10 (13)	–	–
Other glaucoma	1 (1)	–	–
All cases of glaucoma	284 (535)	–	–
Ocular hypertension	21 (32)	0.57 (0.30, 1.10)	0.10

[a] Number of eyes are in parentheses.

with adjustment for gender, age, city and history of cataract surgery and diabetes mellitus. The analyses revealed significant increases in normal-tension glaucoma; the odds ratios at 1 Gy (OR_{1Gy}) were 1.31 (95% CI: 1.11, 1.53, $P = 0.001$) (Table 5 and Fig. 2). Primary angle closure glaucoma showed a suggestive decrease with dose ($OR_{1Gy} = 0.54$, 95% CI: 0.29, 1.02, $P = 0.06$).

Table 6 (Models 1 and 2) indicates regression analyses of risk factors for normal-tension glaucoma. Among the factors, such as city (Nagasaki vs. Hiroshima), gender (female vs. male), age at examination, radiation dose (at 1 Gy), diabetes mellitus, cataract operation in the past and left vs. right eye, statistical significance was observed only for age at examination and radiation. The interaction between age at examination and radiation dose was not significant for normal-tension glaucoma as shown in Model 1 in Table 6. The variables for education, smoking, hypertension and obesity index were added, with results shown as Model 2 in Table 6. The effects of hypertension and the obesity index were significant for normal-tension glaucoma, but after adjustment for all the factors, radiation dose was still statistically significant for normal-tension glaucoma.

DISCUSSION

The prevalence of normal-tension glaucoma significantly increased with increasing A-bomb radiation dose ($P = 0.001$), which appears to be inconsistent with a previous A-bomb survivor study (*8*) and the findings from reported glaucoma treatment in the current study (Table 4). One important difference between the current and previous studies on A-bomb survivors is the diagnostic procedure; diagnoses in the previous study were based on medical history, whereas in the current study they were based on ophthalmologic examination. Elderly survivors may not notice visual disturbances until the symptoms become severe, which could result in false negatives using medical

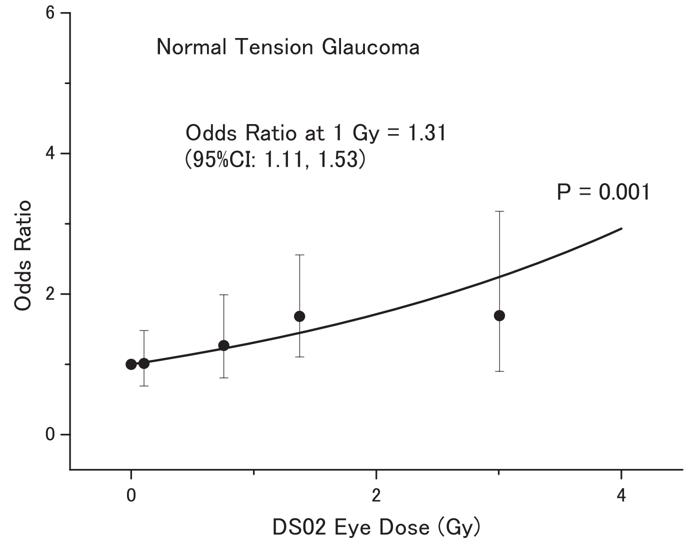

FIG. 2. Relationship between odds ratio of normal-tension glaucoma and radiation dose, OR 1.31 (CI: 1.11, 1.53). Results are based on binary regression analysis using the GEE method with adjustment for gender, age, city, cataract surgery, and diabetes mellitus.

history. Similar to our study, in the Tajimi study only 6.7% of POAG, including normal-tension glaucoma patients, had been previously diagnosed with glaucoma. Glaucoma is a disease in which patients may readily and unknowingly become adapted to progressive visual limitations during the lengthy course of the disease. However, detecting the presence of glaucomatous change is very important even in the early subclinical stage of the disease to effectively treat the disease.

A total of 284 cases were diagnosed as having glaucoma based on ophthalmologic examinations in the current study ($n = 1{,}589$). Only 14% of those had already been diagnosed as part of routine medical or ophthalmological care. Nearly all the newly diagnosed cases were normal-tension glaucoma. This suggests that there is gross underdiagnosis of normal-tension glaucoma in routine medical care settings, and/or that the present study diagnosed numerous cases that are considered subclinical in nature in those settings.

The prevalence of primary open-angle glaucoma (POAG) among A-bomb survivors is higher than that in the Tajimi study (*11, 12*) in all age groups, while those of primary angle-closure glaucoma and of secondary glaucoma are similar to the prevalence in the Tajimi study. In two types of POAG, IOP > 21 mmHg and IOP ≤ 21 mmHg (normal-tension glaucoma), normal-tension glaucoma constitutes 86% of POAG and contributes to the dose-related increase in POAG prevalence in A-bomb survivors. The high prevalence of normal-tension glaucoma, as high as 12.8% in the 0 Gy group (Table 2), indicates that there was a high background prevalence without A-bomb radiation. Possible reasons why we observed a high prevalence of normal-

TABLE 6
Odds Ratio of Various Risk Factors for Normal-Tension Glaucoma

	Odds ratio (95% CI)	P
Model 1[a] (N = 1,589)		
Dose at 1 Gy	1.31 (1.11 1.53)	0.001
City (Nagasaki vs. Hiroshima)	0.78 (0.58 1.04)	0.09
Gender (female vs. male)	0.77 (0.57 1.04)	0.09
Age at examination (given per 10 years at reference age 75)	1.60 (1.29 2.00)	<0.001
Diabetes mellitus	0.73 (0.48 1.09)	0.12
Cataract operation	1.07 (0.80 1.42)	0.65
Eye side (left vs. right)	1.05 (0.99 1.12)	0.14
Model 2 (N = 1,483)		
Dose at 1 Gy	1.33 (1.13 1.57)	0.001
City (Nagasaki vs. Hiroshima)	0.79 (0.58 1.07)	0.12
Gender (female vs. male)	0.72 (0.53 0.99)	0.04
Age at examination (given per 10 years at reference age 75)	1.41 (1.12 1.77)	0.001
Junior high vs. University education[b]	0.89 (0.50 1.57)	0.69
High school vs. University education[c]	1.13 (0.66 1.92)	0.66
Smoking (smoker vs. nonsmoker)	0.70 (0.40 1.26)	0.24
Hypertension (yes vs. no)	1.54 (1.11 2.12)	0.01
Underweight (underweight vs. normal)[d]	1.85 (1.13 3.01)	0.01
Obese (obese vs normal)[d]	1.04 (0.75 1.44)	0.83
Diabetes mellitus (yes vs. no)	0.74 (0.49 1.14)	0.17
Cataract operation (yes vs. no)	1.00 (0.75 1.33)	0.98
Eye side (left vs. right)	1.04 (0.98 1.11)	0.21

Notes. Model 1 used generalized estimating equations (GEE) (*16*) to find the association between glaucoma prevalence in both eyes and explanatory variables, such as city (Nagasaki vs. Hiroshima), gender (female vs. male), age at examination, radiation dose to the eye, diabetes mellitus, cataract surgery and the constant difference of prevalence between eyes (left vs. right). Model 2 included the variables in Model 1, plus additional potential confounding variables, such as education, smoking, hypertension and obesity. Since some variables had missing values, the numbers differ between models (1,589 for Model 1 and 1,483 for Model 2). The STATA statistical package was used for analyses. Two-sided P values and 95% confidence intervals were based on the Wald statistic.

[a] Dose by age at examination interaction was not significant ($P = 0.342$).

[b] Referent category.

[c] Referent category.

[d] Obesity categories: underweight; BMI <18, normal; BMI = 18 – <24, obese; BMI > =24, normal was the referent category.

tension glaucoma in our study include: (1) since all A-bomb survivors are taxied to RERF for the examination, physically poorer individuals, including those with visual disturbances, could be included in our study, whereas in the Tajimi study such support was not available; (2) since the number of participants over age 70 (1,017) in our study is greater than that in the Tajimi study (595), our study could better represent the prevalence in that age category than the Tajimi study; (3) since malnutrition-induced glaucomatous changes have been reported in animals (*17, 18*) and humans (*19*), the same thing could have occurred in A-bomb survivors, many of whom had restricted nutrition during and after the war; and (4) there were several technical differences between the two studies in screening and diagnostic criteria for normal-tension glaucoma.

Only a substantial imbalance in participation related to both radiation exposure and glaucoma status would completely explain the observed odds ratio of 1.31 for normal-tension glaucoma if in fact there were no radiation effect. The evidence of differential participation jointly by radiation dose and glaucoma status is weak at best, so bias in the estimated odds ratio due to nonparticipation is probably small but the uncertainty still mandates some caution in the interpretation. Even though the radiation dose-response slopes for prior glaucoma medication were not statistically significant for either participants or nonparticipants (Table 1), they were not completely parallel: there was a more negative dose-response slope in participants than in nonparticipants ($P < 0.001$). If one were to assume that the more negative dose vs. glaucoma slope for participants compared with nonparticipants was accurate, this would imply there was a negative bias so that the expected association for participants and nonparticipants combined should be even larger than the positive dose-response slope that was found.

A number of other glaucoma risk factors besides radiation were examined as possible confounding factors, including gender, age, city, cataract surgery, diabetes mellitus, education, smoking, hypertension and obesity, but a statistically significant radiation dose-response effect remained for normal-tension glaucoma after adjusting for these factors (Table 6).

The tendency for the prevalence of primary angle-closure glaucoma (PACG) and ocular hypertension to decrease with radiation dose appears consistent with results in animals. The glaucoma-prone DBA/2J mouse is a well-established model of pigmentary glaucoma with higher IOP than normal, and Anderson *et al*. reported that high-radiation doses followed by bone marrow transplant prevented neurodegeneration in DBA/2J mice with inherited glaucoma (*20*).They proposed several possible mechanisms for consideration in regards to radiation protection, including immune alterations and release of trophic factors (*20*). However, a murine pigmentary dispersion model of glaucoma may not be directly relevant to human disease.

The biological mechanism by which ionizing radiation exposure may increase the dose-dependent prevalence of normal-tension glaucoma among A-bomb survivors is not known with certainty. Some possible risk factors to consider may be neuronal excitotoxicity (*21*), inflammation (*22*), genetic predisposition (*23–26*), autoimmunity (*27*) and retinal circulation disturbance (*28, 29*). Among them, we believe that retinal circulation disturbance may be the most likely candidate because there is evidence that radiation induces poor choroidal circulation 30 or 45 years after exposure (*30*), and that retinal arteriolosclerosis in A-bomb survivors is significantly associated with A-bomb radiation 55 years after exposure (*31*). It is possible that radiation eventually causes normal-tension glaucoma through retinal arteriolosclerosis. Studies are under way to confirm this.

In conclusion, our results suggest that the prevalence of normal-tension glaucoma significantly increases with increasing A-bomb radiation dose. However, the large number of study nonparticipants, especially among those with prior glaucoma medication, contributes substantial uncertainty so that caution is required in interpreting the results. Because the present findings are relevant for the radiation safety community, it is important that the issue be examined in other irradiated populations.

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