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Relation Between QT Duration and Mortality in an Elderly Japanese Population

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The effects of prolonged QTc intervals on mortality were investigated in about 3,500 elderly Japanese patients followed for approximately 8.8 years. Prolonged QTc was found to be a marker for risk for all-cause mortality and mortality from heart disease or from coronary heart disease (CHD) after adjusting for other CHD risk factors. Even in Japanese subjects, who have a lower coronary heart disease rate than that of Caucasians, the careful observation of subjects with a prolonged QTc is believed to be necessary. ©2004 by Excerpta Medica, Inc.

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In research involving patients in Western countries, several studies have investigated the association between prolonged QT duration and mortality.[1–3] The Japanese population has a mortality rate of coronary heart disease (CHD) less than half of that of Westerners,[4] indicating a small CHD risk in Japanese subjects. Accordingly, it remains unclear whether prolonged QT duration is a risk for all-cause death and death from heart disease or from CHD in Japanese subjects. Therefore, for the first time, we used electrocardiograms for follow-up examinations of atomic bomb survivors and a control group and investigated whether prolonged QT duration is a risk factor for all-cause mortality, heart disease, or CHD in Japanese subjects.

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The study population was composed of 3,543 subjects, who were not diagnosed as having CHD, atrial fibrillation, atrial flutter, or bundle branch block. They were not taking medications that could cause the prolongation of QT duration at baseline. These subjects were from the Adult Health Study (AHS) of the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki who participated from July 1990 to June 1994 and were followed until death or until December 2000. The cohort was composed of survivors proximally exposed to moderate or large radiation doses, age- and gender-matched survivors distally exposed to small radiation doses, and unexposed controls. The AHS program has already been described in detail elsewhere.[5] At baseline examination, subjects were interviewed and given a structured questionnaire that included a personal medical history, smoking and drinking status, and medication use. They underwent standard 12-lead electrocardiography at rest, and blood samples were obtained. QT intervals were adjusted for heart rate (QTc) according to Bazett's formula.[6] Categories of QTc duration were defined as normal (≤420 ms), moderately prolonged (>420 to 440 ms), and extensively prolonged (>440 ms). The coding of underlying causes of death was performed according to the *International Classification of Diseases-9* (ICD-9) and ICD-10. Deaths were identified through the routine surveillance of information obtained from obligatory family registries. Heart disease was defined as ICD-9 codes 390 to 458, except for 430 to 438, and as ICD-10 codes I00 to I99 and M30, except for I60 to I69. CHD was defined as ICD-9 codes 410 to 414 and ICD-10 codes I20 to I25. The study was approved by the RERF.

CHD risk factors that might be potential confounders were investigated for each of the 3 groups categorized by QTc duration, and all data are expressed as means ± SEs. Categorical data were analyzed by chi-square tests. We conducted analysis of covariance and, if significant, we used the Tukey-Kramer method to assess the relation between QTc duration and CHD risk factors. We used the Cox proportional-hazards model, making the possible assignment of death hazards ratios to the QTc duration categories for prolonged QTc. As potential confounders, we used age, gender, kerma dose of atomic bomb, systolic blood pressure, total cholesterol, body mass index (calculated as body weight [kilograms] divided by the square of standing height [square meters]), a marker of glucose tolerance (HbA1c); and smoking and drinking status, divided into 4 categories: never, ever, current, and missing. Using the DS86 dosimetry system,[7] patient radiation dose was calculated as the sum of γ-rays and neutron kerma. For the Cox proportional-hazards model, proportional hazards assumptions for categories of QTc duration were verified by the inspection of log–log survival curves. For all data analysis, SAS (SAS Institute, Cary, North Carolina) procedures were used.

Clinical characteristics of the subjects categorized according to QTc duration at baseline, adjusted for gender, are shown in Table 1. Mean age was 65.0 ± 0.2 years (range 45 to 98). In the investigation of the 3 QTc categories, compared with the normal QTc group, the moderately prolonged QTc group and the extremely prolonged group had, respectively: all-cause mortality hazard ratios (HRs) of 1.28 (95%

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TABLE 1 Clinical Characteristics at Baseline

Variable	QTc (ms) ≤420 (n = 1,884 [53.2%])	420–440 (n = 965 [27.2%])	>440 (n = 694 [19.6%])
Men/women	826/1058	236/729	120/574
Number of current smokers (%)	468 (24.8)	187 (19.4)	96 (13.8)
Death	275	172	146
Heart disease (CHD)	39 (14)	39 (13)	39 (15)
Age (yrs)	63.6 ± 0.2	65.0 ± 0.3*	66.5 ± 0.4*
Body mass index (kg/m^2)	22.8 ± 0.1	22.8 ± 0.2	23.2 ± 0.1*
Systolic blood pressure (mm Hg)	129 ± 1	133 ± 1*	138 ± 1*
Diastolic blood pressure (mm Hg)	78 ± 0	80 ± 0	82 ± 0*
HbA1c (%)	5.78 ± 0.02	5.81 ± 0.03	5.84 ± 0.04
Total cholesterol (mmol/L)	5.51 ± 0.02	5.49 ± 0.03	5.35 ± 0.04

Data are expressed as means ± standard errors after adjustment for gender.
*Significantly different from QTc of ≤420 ms (Tukey-Kramer test, p <0.05).

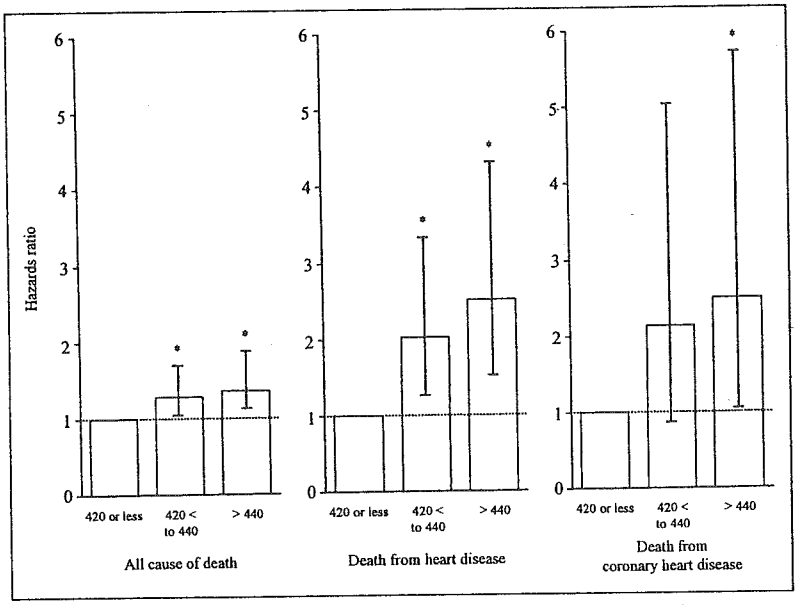

FIGURE 1. HR of mortality from a Cox proportional-hazards model according to baseline QTc duration. Data were expressed after the adjustment of age, gender, kerma dose of atomic bomb, systolic blood pressure, total cholesterol, body mass index, HbA1c, and smoking and drinking status. *Error bars*, 95% CIs. Trend analysis was p = 0.005 for all-cause death, p = 0.0003 for death from heart disease, and p = 0.034 for death from CHD. *p <0.05 compared with the normal QTc category.

confidence interval [CI] 1.04 to 1.58) and 1.36 (95% CI 1.08 to 1.70), HRs for mortality from heart disease of 2.02 (95% CI 1.22 to 3.34) and 2.51 (95% CI, 1.51 to 4.17), and mortality from CHD of 2.13 (95% CI 0.90 to 5.03) and 2.49 (95% CI 1.05 to 5.88), after adjustment was made for all potential confounders. Moreover, it was observed that when QT duration was prolonged, the HR of all-cause death and death from heart disease or CHD tended to increase significantly (p = 0.005, 0.0003, and 0.034, respectively), even when adjusted for all confounders (Figure 1). From these data, QTc prolongation was a significant risk factor for all-cause mortality and mortality from heart disease or from CHD. Regarding other risk factors for all causes of death, significant variables were age, gender, kerma dose of atomic bomb, HbA1c, current smoking, systolic blood pressure, and total cholesterol. For heart disease, significant variables were age, HbA1c, current drinking, and current smoking. For CHD, significant variables were age and HbA1c (Table 2). On the basis of these data, radiation dose had no effect on death from heart disease or CHD, but in terms of CHD, it was believed that prolonged QTc was as much a prognostic factor as HbA1c. In all analyses, no interaction was observed between gender and each category of QTc duration.

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Among studies of Westerners, some indicate that prolonged QTc duration is a risk factor for all-cause mortality, sudden death, and cardiovascular disease. However, the rate of CHD in Japanese subjects is lower than that in Western populations, leading to a situation in which no studies have been conducted on the effects of prolonged QTc on all-cause mortality and death from heart disease or from CHD in Japanese subjects. In this study, we investigated such effects in an elderly population of Japanese patients. Even in the Japanese population, prolonged QTc was found to be a marker for risk for all-cause mortality and mortality from heart disease or from CHD, even after adjusting for other CHD risk factors.

Age, gender, systolic blood pressure, total cholesterol, glucose intolerance indicated by HbA1c, and smoking and drinking status have been reported as risk factors for CHD.[8–15] In our study, in addition to increased QTc, HbA1c (a marker of glucose tolerance), systolic blood pressure (a marker of hypertension), and current smoking increased the risk for all-cause death. In terms of death from heart disease or CHD, the small number of cases led to the observation that some of these factors were no longer significant. However, the same tendency of increased risk existed, with the HR for each of the parameters. Even after adjusting for these risk factors, we found that the prolongation of QTc duration was strongly associated with all-cause mortality and mortality from heart disease or from CHD, and the HR was greater in the groups with greater QTc prolongation (Table 2). These results suggest that prolonged QTc was as important a prognostic factor as HbA1c, systolic blood pressure, and smoking for all-cause death, and HbA1c in cases of death from CHD. In addition, because exposure dose was not a significant risk factor for death from heart disease or CHD, there was believed

TABLE 2 Hazard Ratios of Death from a Cox Proportional-hazards Model

Variable	All-cause Death Hazard Ratio (95% CI) p Value	Death from Heart Disease Hazard Ratio (95% CI) p Value	Death from CHD Hazard Ratio (95% CI) p Value
Age (per 1 year)	1.10 (1.09–1.11) <0.0001	1.13 (1.10–1.16) <0.0001	1.15 (1.10–1.20) <0.0001
Sex (men vs women)	1.98 (1.55–2.53) <0.0001	1.34 (0.74–2.44) 0.329	1.58 (0.59–4.28) 0.365
Kerma dose of atomic bombs (per 1 Gy)	1.00 (1.00–1.00) 0.003	1.00 (1.00–1.00) 0.312	1.00 (0.99–1.00) 0.680
HbA1c (per 1%)	1.33 (1.24–1.43) <0.0001	1.42 (1.24–1.63) <0.0001	1.60 (1.31–1.96) <0.0001
Current drinking (vs never)	0.88 (0.68–1.13) 0.311	0.40 (0.21–0.76) 0.006	0.40 (0.13–1.19) 0.099
Current smoking (vs never)	1.66 (1.25–2.20) 0.0004	1.97 (1.01–3.83) 0.045	2.14 (0.66–6.90) 0.204
Body mass index (per 1 kg/m^2)	0.98 (0.95–1.01) 0.116	0.97 (0.92–1.03) 0.359	1.01 (0.91–1.11) 0.868
Systolic blood pressure (per 1 mm Hg)	1.01 (1.00–1.01) 0.005	1.01 (0.99–1.02) 0.101	1.01 (0.99–1.03) 0.216
Total cholesterol (per 1 mmol/L)	0.99 (0.99–1.00) <0.0001	1.00 (0.99–1.01) 0.773	1.00 (0.99–1.01) 0.471

Hazard ratios (95% CIs) of Cox proportional-hazards model as independent variables accounting for death.

to be no association between dose and the deaths from these diseases.

The prolongation of QTc duration indicates subclinical imbalance in the autonomic nervous system that has important effects on ventricular repolarization.[3,16,17] Prolonged QTc duration may cause an increase in deaths from ischemic heart disease due to an increased susceptibility to malignant ventricular arrhythmias. Therefore, the prolongation of QTc duration in our study population indicated an attenuation of cardiac sympathetic nervous system function and may have affected death from heart disease or from CHD.

Our study found no statistical interaction between QTc and gender, and it appeared that there was no gender difference with respect to the effects of QTc on mortality. Our study therefore analyzed men and women together. In our study and previous studies conducted in the Western countries,[1–3,18,19] the mean ages and durations of observations differ. In the studies carried out in Western countries, the mean age was relatively young; subjects were generally ≤50 years of age. Moreover, the period of observation was >20 years. In contrast, our study followed a group of Japanese subjects with a mean age of >60 years and had an average period of observation of 8.79 ± 0.03 years. These differences in the subjects of each of these studies are believed to have played a role in the varying results obtained. Comparison of the results, therefore, must be made carefully.

We investigated the effects of QTc duration on mortality in a cohort population of elderly Japanese. In the Japanese population, because a positive trend between QTc duration and mortality from heart disease was observed, it must be recognized that QTc prolongation is a risk factor for mortality from heart disease, even when that prolongation is moderate (Figure 1; Table 2). These results suggest that Japanese subjects with prolonged QTc duration are at great risk for death from CHD and thus require careful follow-up.

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Noncancer Disease Incidence in Atomic Bomb Survivors, 1958–1998

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Yamada, M., Wong, F. L., Fujiwara, S., Akahoshi, M. and Suzuki, G. Noncancer Disease Incidence in the Atomic Bomb Survivors, 1958–1998. *Radiat. Res.* 161, 622–632 (2004).

We examined the relationships between the incidence of noncancer diseases and atomic bomb radiation dose using the longitudinal data for about 10,000 Adult Health Study (AHS) participants during 1958–1998. The current report updates the analysis we presented in 1993 with 12 additional years of follow-up. In addition to the statistically significant positive linear dose–response relationships detected previously for the incidence of thyroid disease ($P < 0.0001$), chronic liver disease and cirrhosis ($P = 0.001$), and uterine myoma ($P < 0.00001$), we also found a significant positive dose response for cataract ($P = 0.026$), a negative linear dose–response relationship for glaucoma ($P = 0.025$), and significant quadratic dose–response relationships for hypertension ($P = 0.028$) and for myocardial infarction among survivors exposed at less than 40 years of age ($P = 0.049$). Significant radiation effects for calculus of the kidney and ureter were evident for men but not for women (test of heterogeneity by sex: $P = 0.007$). Accounting for smoking and drinking did not alter the results. Radiation effects for cataract, glaucoma, hypertension, and calculus of the kidney and ureter in men are new findings. These results attest to the need for continued follow-up of the aging A-bomb survivors to fully elucidate the effects of radiation exposure on the occurrence of noncancer diseases.

INTRODUCTION

The Adult Health Study (AHS) was begun in 1958 by the Atomic Bomb Casualty Commission (ABCC), succeeded in 1975 by the Radiation Effects Research Foundation (RERF), as biennial clinical examinations of a subset of the Life Span Study (LSS) cohort to examine the late effects of atomic bomb exposure. The 1993 report (*1*) showed for the first time that the incidence of uterine myoma, chronic liver disease and cirrhosis, and thyroid disease increased with radiation dose during 1958–1986, confirming some of the impressions from an earlier prevalence study (*2*). The current report, covering 40 years between 1958–1998, updates the first incidence study results with 12 additional years of follow-up and two more diseases. Cigarette smoking and alcohol consumption were also examined as potential confounders and as dose–response modifiers.

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MATERIALS AND METHODS

Study Population

The AHS was established in 1958 as a subset of the LSS cohort, comprising 19,961 Hiroshima and Nagasaki subjects. The AHS biennial health examinations presented clinical information complementary to the LSS death and tumor registries data. To enhance detection of radiation effects, the AHS included disproportionately more individuals exposed at higher doses than were present in the LSS: about half were within 2 km of the hypocenter (proximal exposure), a quarter were at distances over 3 km (distal exposure), and a quarter were not in city (NIC) at the time of bombing (ATB).

The study subjects attended at least two examinations between July 1, 1958 and June 30, 1998. This report uses data from 10,339 subjects (2.2×10^5 person-years of follow-up), which is the original cohort reduced by 5,000 NIC subjects, 2,064 who lacked Dosimetry System 86 (DS86) dose estimates (*3*), and 2,558 who attended fewer than two examinations. Compared to the 1993 report (*1*), an additional 698 subjects and 3×10^4 person-years (15.8%) are represented here. Since case identification relied on the biennial health examinations, the AHS data are qualitatively different from those of the LSS mortality and tumor registry program.

Sixty-three percent of the subjects were women and 73% were Hiroshima residents (Table 1). About 50% of the AHS subjects had died by July 1998. The proportion of participants who were under 20 years of age ATB increased from 1/3 in 1958–1960 to 60% in 1996–1998, reflecting age-related mortality. Conversely, those over 40 years ATB decreased from 29% in 1958–1960 to 2% in 1996–1998. A high participation rate (75 to 90%) was maintained throughout the examinations for study subjects living in Hiroshima and Nagasaki and their neighboring towns. More than half had attended 11 or more examinations.

A subject's follow-up began at the initial AHS visit and ended on the earlier of the date of the last disease-free visit or the date of the disease onset. The disease onset date was estimated as the midpoint between the first disease diagnosis date and the date of the previous disease-free examination. For each disease, cases present at the initial visit were excluded.

Clinical Procedures and Selection of Diseases for Study

The biennial health examinations, conducted with informed consent, consist of history-taking, physical examination, and laboratory tests. Details are available elsewhere (*1, 2*). Incident cases were ascertained by scanning for the first occurrence of the three-digit International Classification of Diseases (ICD) (*4*) codes stored in the AHS database. The ICD codes of the 21 diseases examined are listed in the Appendix. At each examination, the first three digits of the ICD codes, up to six diagnoses

TABLE 1
Distribution of the 10,339 AHS Participants by DS86 Weighted Total Shielded Kerma Categories (Sv)

		DS86 categories (RBE = 10) in Sv							
	Total	0.0	0.001–0.49	0.5–0.99	1.0–1.49	1.5–1.99	2.0–2.49	2.5–2.99	3.0+
Hiroshima	7575	2750	2541	941	454	252	193	131	314
Men	2698	1004	823	335	174	102	77	48	136
Women	4877	1746	1718	606	280	150	116	83	178
Mean dose	0.57	0	0.21	0.72	1.23	1.75	2.24	2.75	4.14
Mean age ATB	30.6	30.4	31.2	31.3	30.7	31.2	29.0	29.2	27.2
Nagasaki	2764	1205	532	345	338	166	76	35	67
Men	1111	514	192	125	129	75	32	14	30
Women	1653	691	340	220	209	91	44	21	37
Mean dose	0.58	0	0.22	0.76	1.23	1.74	2.18	2.70	3.83
Mean age ATB	24.5	24.2	26.5	24.5	24.1	23.8	23.3	22.4	22.1
Total	10,339	3954	3073	1286	792	418	269	166	381

per person, were stored before June 1986; four-digit codes, up to 12 per person, were stored thereafter. Medical charts and death certificates were not reviewed for case validation.

Radiation Dosimetry

We used individual estimates of kerma and organ-specific dose in which survivor location and shielding by terrain and the body are taken into account based on the DS86. Kerma and organ doses, both expressed in sieverts, were calculated as weighted sums of their γ-ray and neutron components in grays, giving the neutron component a weight of 10. Before weighted sums were calculated, DS86 kerma estimates were truncated to 4 Gy, in consideration of the imprecision in dose assessment for proximal survivors (*5*). The estimated organ doses were adjusted for random dosimetry error, generally thought to be about 35%, to reduce bias in risk estimates (*5–7*). We used thyroid dose for the analysis of thyroid diseases, eye dose for eye diseases, liver dose for liver disease, uterine dose for gynecological diseases, bladder dose for prostate disease, and stomach dose for all others. Our 1993 report (*1*) used unweighted organ-specific doses for thyroid diseases, eye diseases, liver disease, gynecological diseases, prostate disease, and gastrointestinal diseases, and unweighted shielded kerma for residual diseases, with truncation to 6 Gy instead of 4 Gy and without adjustment for random dosimetry errors. As a result, the individual dose estimates used here were generally lower compared to those of the previous report.

Table 1 shows the distribution of the AHS participants by DS86 categories. Nearly 20% of the cohort had exposure doses of 1 Sv or more. The mean weighted shielded kerma was 0.57 Sv ± 0.94 [standard deviation of the mean (SD)]. The unexposed category (doses = 0) includes 38.2% of the study cohort. Among the exposed (doses > 0), the mean weighted shielded kerma was 0.92 Sv ± 1.06.

Cigarette Smoking and Alcohol Consumption

Cigarette smoking history was abstracted from four LSS mail surveys (administered to men in 1965, to women in 1969–1970, to both men and women in 1979–1980 and in 1991) and one survey administered during the AHS examinations of 1965–1966. All AHS participants were part of the pre-1991 surveys, but only about 15% were part of the 1991 survey. The response rate was over 95% for all surveys. Smoking and drinking statuses were considered as time-varying covariates. Follow-up time was classified as "never smoked", "smoke currently" or "smoked in the past" according to changes in smoking status. We also used composite classification of "never smoked" and "ever smoked" for descriptive purposes. Among men, 11% never smoked, 79% smoked at some time, and 10% had no smoking information. Among women, 72% never smoked, 18% smoked at some time, and 10% had no smoking information.

We obtained alcohol intake information from two LSS mail surveys in 1979–1980 and 1991 and from the AHS epidemiological survey of 1965–1966. The classification scheme used for smoking was applied to alcohol. Among men, 16% never drank, 70% drank at some time, and 14% had no data. Among women, 63% never drank, 26% had drunk at some time, and 11% had no data. Due to lack of timely information, nonsmoking and nondrinking groups most likely included actual smokers and drinkers.

There was no significant difference in dose among the smoking and drinking classes except for smoking in women: The mean dose was significantly higher by 15% for ever-smokers than for never-smokers ($P < 0.01$).

The background disease incidence rates were significantly higher for "ever smoked" than for "never smoked" subjects for cardiovascular disease, gastric ulcer, chronic liver disease, and cholelitiasis. However, the background risk of cataract was significantly lower among the "ever smoked". Alcohol-related increase in risk was found for chronic liver disease, and protective effects were observed for hyperplasia of the prostate and Parkinson's disease.

Statistical Methods

We applied Poisson regression methods for the longitudinal analysis of incidence data, using AMFIT of the EPICURE program package (*8*). We stratified disease incidence rates by city (Hiroshima, Nagasaki), sex (male, female), age ATB in years (upper bounds: 10, 20, 30, 40, 50, 60, 60+), age at examination (age ATE) in years (upper bounds: 20, 30, 40, 50, 60, 70, 80, 80+), calendar time (July 1, 1958–December 31, 1967; January 1, 1968–December 31, 1977; January 1, 1978–December 31, 1987; January 1, 1988–June 30, 1998), and DS86 total weighted organ dose in sieverts (upper bounds: 0, 0.5, 1.0, 1.5, 2.0, 3.0, 3.0+). For some analyses, cigarette smoking (never smoked, smoke currently, smoked in the past) and alcohol intake (never drank, drink currently, drank in the past) were also included as time-varying covariates in disease rate stratification. The number of disease cases in each stratum was assumed to be an independent Poisson variate with mean $PY_{ij}\gamma_{ij}$, where PY_{ij} is person-years and γ_{ij} is disease incidence rate in the jth dose category and the ith category defined by other cross-classifications. γ_{ij} may also be represented by $\gamma_{ij} = \gamma_{i0}\,RR_{ij}$, where γ_{i0} is the incidence rate in stratum i in the absence of radiation exposure and RR_{ij} is the relative risk due to radiation dose associated with the jth exposure level. We assumed an additive linear dose–response model: $RR_{ij} = 1 + \beta d_{ij} \exp[\alpha_k(Z_k)]$, where d_{ij} is the jth dose level in stratum i, β is the excess risk per sievert averaged over all strata, and z_k represents the effect modifiers. We used the mean dose in each ijth stratum for d_{ij}. For diseases with a significant linear dose effect (β), the presence of curvature was assessed by the significance of η in the linear-quadratic model, $RR_{ij} = 1 + \beta d_{ij} + \eta d_{ij}^2$. We also examined purely quadratic effects for all diseases by testing the significance of η in the model $RR_{ij} = 1 + \eta d_{ij}^2$. We used a two-sided type I error of 0.05.

TABLE 2
Number of Disease Cases and Observed Background Incidence

Disease	No. of cases		Background incidence per 10,000 PY				
			Crude rates			Standardized rates[a]	
	Male	Female	Total	Male	Female	Male	Female
Hypertension	1792	3243	286.44	304.33	276.92	178.2	185.2
Hypertensive heart disease	585	1301	80.73	80.13	81.06	38.0	42.3
Ischemic heart disease	600	946	63.40	76.10	56.67	31.5	27.3
Myocardial infarction	65	52	5.36	9.88	2.94	4.0	1.3
Occlusion, stenosis	232	208	17.69	27.46	12.47	9.9	5.5
Aortic aneurysm	74	110	6.78	9.88	5.12	3.8	2.4
Stroke I	272	259	20.79	30.76	15.47	11.3	6.9
Stroke II	356	373	27.98	41.01	21.04	15.7	9.6
Thyroid disease	182	782	36.99	19.82	46.66	12.9	48.5
Cataract	975	2509	154.25	123.01	171.98	53.8	97.9
Gastric ulcer	476	454	37.45	60.23	25.81	37.2	15.5
Duodenal ulcer	219	152	14.46	25.96	8.47	22.3	6.3
Chronic liver disease and cirrhosis	785	989	71.66	93.72	60.32	59.2	35.2
Cholelithiasis	271	688	40.64	35.59	43.38	16.3	22.6
Calculus of kidney and ureter	170	153	11.02	16.47	8.1	8.8	5.0
Uterine myoma	—	922	51.68	—	51.68	—	37.7
Cervical polyp	—	281	15.48	—	15.48	—	11.8
Hyperplasia of prostate	461	—	60.68	60.68	—	22.7	—
Dementia	79	237	11.32	6.36	13.99	2.3	6.7
Parkinson's disease	35	62	3.12	4.05	2.63	1.5	1.3
Glaucoma	52	159	10.16	6.67	12.03	2.9	5.4

[a] Directly standardized to the Japanese population of 1985.

The reference group consisted of 3954 persons with DS86 dose estimates of zero.

We evaluated the significance of the effect modifiers (city, sex, age ATB, age ATE, calendar time, smoking and drinking) for the diseases for which the main effects of radiation were significant or suggestive. Generally, covariates were treated as categorical except for age ATB and age ATE, for which we used the cell-specific means. We used the likelihood ratio method for significance testing and for computing the 95% confidence intervals.

RESULTS

The number of disease cases and the background incidence rates for the 21 diseases are shown in Table 2. We estimated the background rates using the unexposed subjects. We calculated the standardized rates using the Japanese population of 1985 (*9*), as in the previous report (*1*). The standardized rates increased for only dementia and Parkinson's disease, in spite of the aging of the population and implementation of more specific diagnostic procedures such as ultrasonography.

Table 3 shows the estimated relative risk at 1 Sv (RR_{1Sv}), the average excess disease per 10^4 PY Sv, and the attributable risk based on the linear model. Attributable risk is the percentage of the disease cases due to over 0.001 Sv of exposure. The last two columns also show the significance level and the RR_{1Sv} obtained by further stratifying the background rates by smoking and drinking. Between 1958–1998, a significant linear increase with radiation dose ($P < 0.05$) was detected for the incidence of thyroid diseases, chronic liver disease and cirrhosis, uterine myoma, and cataract and was suggested for calculus of the kidney and ureter ($P = 0.07$). A significant linear decrease was detected for the incidence of glaucoma. There was no indication of a curvilinear increase/decrease in risk at high doses for these diseases. The fitted linear models and the estimated relative risks are shown in Fig. 1. The relative risk estimate for uterine myoma at over 3 Sv was omitted, since only three women had that exposure level. A nonlinear dose–response relationship was evident for hypertension (Fig. 2A). Significant radiation effects were not detected for other cardiovascular diseases, including MI. However, in accord with our previous results (*1*), MI incidence during 1968–1998 for survivors under 40 years ATB ($MI^{<40}$, 78 cases) showed a significant curvilinear dose–response relationship (Fig. 2B). Adjustment for smoking and drinking only slightly affected the significance level of the linear dose response for hypertension and calculus of the kidney and ureter. The results of the examination of city, sex, age ATB, age ATE, and calendar time as modifiers of the dose–response relationship are shown in Table 4; significant or suggestive evidence of radiation effects is shown in the results for each disease.

Thyroid Disease

The relative risk at 1 Sv (RR_{1Sv}) for thyroid disease was 1.33 ($P < 0.0001$, 95% CI: 1.19–1.49). The average number of excess disease cases per 10^4 PY Sv was 12, and the attributable risk was 18%. These estimates are similar to

those obtained previously (*1*), which were based on 13.5% fewer cases.

Radiation risk was higher for subjects exposed at younger ages and for subjects examined at younger ages. With age ATB included as the most significant effect modifier, age ATE was not additionally significant ($P = 0.58$), indicating age ATB as the stronger factor. In fact, increased radiation risk was apparent for survivors exposed at less than 20 years of age ($P < 0.0001$, $RR_{1Sv} = 1.54$, 95% CI: 1.33–1.81) but not for those exposed at older ages ($P = 0.18$, $RR_{1Sv} = 1.11$, 95% CI: 0.96–1.30).

Chronic Liver Disease and Cirrhosis

RR_{1Sv} for liver disease was 1.15 ($P = 0.001$, 95% CI: 1.06–1.25). The average excess risk was 11 cases per 10^4 PY Sv and the attributable risk was 8%. Similar estimates were obtained in our previous report, with 42% fewer cases. The effect modifiers were not significant.

The ICD code for chronic liver disease (571) includes alcoholic liver disease (571.1–571.3), chronic hepatitis (571.4), cirrhosis without mention of alcohol (571.5), biliary cirrhosis (571.6), and other chronic nonalcoholic liver disease (571.8). The use of the four-digit ICD after June 1986 resulted in a large increase in cases after June 1986, due mainly to nonalcoholic fatty liver (571.8) detected by ultrasonography, comprising 69% of the incident cases. Ultrasonography began to be used in the Hiroshima laboratory in 1981 and in the Nagasaki laboratory in 1984. Participation in ultrasonography was voluntary before 1991, raising the possibility of dose-related bias. Ultrasonography has been performed routinely since 1991, resulting in a dramatic rise in fatty liver diagnoses, but diagnoses of other chronic liver diseases did not change noticeably.

We examined radiation effects for fatty liver alone and for all other chronic liver diseases occurring after 1986. For all liver diseases, there was significant linear dose response ($P = 0.054$, $RR_{1Sv} = 1.14$, 95% CI: 1.0–1.32). No significant heterogeneity in the risk estimates was observed before and after June 1986 ($P = 0.76$). For fatty liver alone (445 cases), a linear dose response was suggested ($P = 0.073$, $RR_{1Sv} = 1.16$, 95% CI: 0.99–1.37). For 199 cases of other chronic liver diseases, radiation effects were nonsignificant ($RR_{1Sv} = 1.06$, $P = 0.64$, 95% CI: 0.84–1.40).

Uterine Myoma

RR_{1Sv} for uterine myoma was 1.46 ($P < 0.00001$, 95% CI: 1.27–1.67). There were 25 excess cases per 10^4 PY Sv, and the attributable risk was 19%. Similar estimates were obtained previously (*1*), with 23% fewer cases. Much of the increase in cases could be attributed to the use of ultrasonography.

Radiation risk varied significantly by calendar time or, equivalently, time since exposure ($P = 0.015$) and by age ATB ($P = 0.042$). The risk decreased steadily in the first three decades of follow-up ($RR_{1Sv} = 2.0$, 1.7, 1.1), which was noted in our previous report (*1*), then increased slightly in the fourth decade ($RR_{1Sv} = 1.3$).

Years since exposure was the most significant effect modifier compared to age ATB and age ATE. Neither age ATB ($P = 0.75$) nor age ATE ($P = 0.75$) was additionally significant with years since exposure included as dose–effect modifier.

We also found that radiation risk was elevated for the exposed nondrinkers ($P < 0.0001$, $RR_{1Sv} = 1.62$, 95% CI: 1.36–1.94), but not for exposed drinkers ($P < 0.50$, $RR_{1Sv} = 1.09$, 95% CI: 0.86–1.40) (test of heterogeneity, $P = 0.011$).

Cataract

We detected a significant positive linear dose–response relationship ($P = 0.026$, $RR_{1Sv} = 1.06$, 95% CI: 1.01–1.11). The estimated number of excess cataract cases per 10^4 PY Sv was 8, and the attributable risk was 4%. Radiation risk varied significantly by age ATE ($P < 0.001$) and possibly by follow-up period ($P = 0.09$). A decreasing trend for the first three decades was observed here as well as in the previous report, although RR_{1Sv} increased to 1.08 in the most recent decade. Considered simultaneously with age ATE as effect modifier, follow-up period was also significant ($P = 0.012$), but their interaction was not ($P = 0.78$). Since lens opacities surge after age 60 years (*11*), we looked for heterogeneity in the dose response between age ATE ≤ 60 and >60 years. Radiation effects were significant for the younger group ($P = 0.009$, $RR_{1Sv} = 1.16$, 95% CI: 1.04–1.32) but not for the older group ($P = 0.24$, $RR_{1Sv} = 1.03$, 95% CI: 0.98–1.09) (test of heterogeneity: $P = 0.08$).

Glaucoma

Examined for the first time in this report, glaucoma showed a significant negative dose–response relationship ($P = 0.025$, $RR_{1Sv} = 0.82$, 95% CI: 0.80–0.97). The lower 95% confidence bound was the lowest value feasible before RR became negative. There was a deficit of -1.5 glaucoma cases per 10^4 PY Sv, and rates were reduced by 15% for subjects exposed to over 0.001 Sv. The dose–response relationship was not modified by the covariates considered.

Since rural/urban variation in baseline disease rates could bias radiation risk estimates (*12*), distal/proximal exposure indicator was used as a surrogate for adjustment. This resulted in a lack of dose response ($P = 0.14$), with RR_{1Sv} essentially unchanged.

Hypertension

Radiation effects were not evident under the linear dose–response model ($P = 0.15$), but they were significant under the purely quadratic model ($P = 0.028$, $RR_{1Sv} = 1.03$, 95% CI: 1.00–1.06) (Fig. 2A). Based on the quadratic model, there were seven excess hypertension cases per 10^4 PY Sv, and 2% were attributed to radiation exposure. Incident cases increased by 16% since the previous report. There was

TABLE 3
Linear Dose Response for Noncancer Disease Incidence between 1958 and 1998 in Hiroshima and Nagasaki Men and Women, Stratified by City, Sex, Age ATB, Age ATE, and Calendar Time

Disease	No. cases	Without smoking and drinking in stratification	
		P	Estimated RR at 1 Sv
Hypertension	5035	0.14	1.04 (0.99, 1.09)[b]
Hypertension[f]	5035	0.028	1.03 (1.00, 1.06)
Hypertensive heart disease	1886	0.86	1.01 (0.92, 1.10)
Ischemic heart disease	1546	0.47	1.04 (0.94, 1.14)
Myocardial infarction[d]	117	0.38	1.11 (0.90, 1.46)
Myocardial Infarction$^{<40}$[g]	78	0.05	1.25 (1.00, 1.69)
Occlusion, stenosis	440	0.61	1.05 (0.88, 1.27)
Aortic aneurysm	184	0.74	1.05 (0.88, 1.44)
Stroke I	531	0.52	1.05 (0.90, 1.25)
Stroke II	729	0.43	1.06 (0.92, 1.23)
Thyroid disease	964	0.0000	1.33 (1.19, 1.49)
Cataract	3484	0.026	1.06 (1.01, 1.11)
Gastric ulcer	930	0.98	1.00 (0.89, 1.13)
Duodenal ulcer	371	0.54	0.95 (0.81, 1.14)
Chronic liver disease and cirrhosis	1774	0.0010	1.15 (1.06, 1.25)
Cholelithiasis	959	0.93	1.00 (0.89, 1.12)
Calculus of kidney and ureter	323	0.07	1.19 (0.98, 1.46)
Uterine myoma (females)	922	0.0000	1.46 (1.27, 1.67)
Cervical polyp (females)	281	0.29	1.14 (0.90, 1.48)
Hyperplasia of prostate (males)	461	0.26	0.91 (0.79, 1.07)
Dementia	316	0.22	1.17 (0.91, 1.52)
Parkinson's disease	97	0.98	1.00 (0.72[c], 1.55)
Glaucoma	211	0.025	0.82 (0.80[c], 0.97)

[a] Average PY: total = 2.2×10^5 PY; male = 8.1×10^4 PY; female = 1.5×10^5 PY (actual numbers depend on the disease).
[b] 95% confidence interval.
[c] Minimum feasible value.
[d] Incidence after June 30, 1964, since no ICD codes for MI were available before 1964.
[e] Based on Wald's confidence interval; no feasible likelihood-based upper bound could be estimated.
[f] Based on the quadratic dose–response model.
[g] Based on the quadratic dose–response model, for incidence during 1968–1998 and age ATB under 40 years.

suggestive evidence ($P = 0.07$) for increased hypertension risk for exposed nonsmokers ($RR_{1Sv} = 1.04$) but not for exposed smokers ($RR_{1Sv} = 1.00$). The dose response was not modified significantly by other covariates.

Cardiovascular Diseases

None of the cardiovascular diseases showed a significant relationship with radiation dose. The linear dose response was not significant for overall MI ($P = 0.38$) and MI$^{<40}$ incidence ($P = 0.10$), but a significant quadratic relationship was evident for MI$^{<40}$ ($P = 0.05$, $RR_{1Sv} = 1.25$, 95% CI: 1.00–1.69) (Fig. 2B). Under the quadratic model, the number of excess MI$^{<40}$ cases per 10^4 PY Sv is one and 16% were attributed to radiation exposure.

Calculus of the Kidney and Ureter

An overall linear dose response was suggestive ($P = 0.07$): It was significant for men ($RR_{1Sv} = 1.47$, 95% CI: 1.13–1.96) but not for women ($RR_{1Sv} = 0.86$, 95% CI: 0.73–1.17) (test of heterogeneity: $P = 0.007$). The dose response disappeared after adjustment for smoking and drinking ($P = 0.13$), but radiation effects remained significant for men even after adjustment. Subjects exposed at an early age ($P = 0.0008$, $df = 2$) and examined at a younger age ($P = 0.019$, $df = 2$) showed higher radiation risks. Age ATB was the most significant effect modifier in the overall analysis as well as in the male-specific analysis.

DISCUSSION

Thyroid Disease

Radiation-related thyroid abnormalities continued to occur in the extended follow-up period. Although malignant and benign thyroid tumors increased with A-bomb radiation dose (*10, 11*), radiation effects on specific thyroid disorders could not be assessed here because a large percentage of cases had multiple thyroid abnormalities, and thyroid function tests and ultrasonography were not administered routinely.

The latest AHS thyroid disease prevalence study in Nagasaki applying uniform diagnostic criteria (ultrasonography, thyroid function test, and autoimmune antibody) revealed a significant dose response for solid nodules in women, especially those exposed at young ages, and a con-

TABLE 3
Extended

Without smoking and drinking in stratification		With drinking and smoking in stratification	
Average excess disease × 10^4 PY Sv[a]	Attributable risk (%)	*P*	Estimated RR at 1 Sv
10.59 (−3.41, 24.63)	2.2 (−0.7, 5.0)	0.08	1.05 (0.99, 1.10)
7.26 (0.76, 14.06)	1.8 (0.2, 3.6)	0.01	1.03 (1.01, 1.06)
0.61 (−5.92, 7.48)	0.42 (−4.2, 5.2)	0.87	0.99 (0.91, 1.09)
2.13 (−3.47, 8.10)	1.5 (−3.2, 6.5)	0.33	1.05 (0.95, 1.16)
0.57 (−0.59, 1.64)	8.5 (−8.8, 24.5)	0.48	1.12 (0.84, 1.60)
1.03 (0.01, 13.84)	15.6 (0.03, 30.8)	0.14	1.17 (0.97, 1.56)
0.76 (−2.00, 3.82)	2.5 (−6.6, 12.6)	0.52	1.06 (0.89, 1.30)
0.34 (−1.41, 2.49)	2.5 (−11.0, 18.9)	0.90	1.02 (0.78, 1.41)
1.05 (−2.02, 4.50)	2.8 (−5.4, 12.1)	0.41	1.08 (0.90, 1.31)
1.57 (−2.21, 5.84)	3.0 (−4.2, 11.2)	0.40	1.07 (0.92, 1.24)
11.99 (7.43, 16.32)	18.5 (11.5, 25.2)	<0.0001	1.38 (1.22, 1.57)
7.98 (0.95, 15.16)	3.8 (0.4, 7.2)	0.004	1.11 (1.03, 1.19)
−0.038 (−4.44, 4.76)	−0.06 (−6.5, 7.0)	0.89	1.00 (0.88, 1.12)
−0.89 (−3.38, 2.09)	−3.4 (−12.7, 7.8)	0.69	0.96 (0.82, 1.16)
10.90 (4.25, 17.79)	8.1 (3.2, 13.2)	0.0087	1.12 (1.03, 1.22)
−0.19 (−4.43, 4.31)	−0.3 (−6.6, 6.4)	0.94	1.00 (0.89, 1.12)
2.41 (−0.21, 5.39)	9.8 (−0.9, 21.9)	0.13	1.16 (0.96, 1.43)
25.02 (15.68, 34.66)	18.9 (11.8, 26.2)	<0.0001	1.39 (1.22, 1.60)
2.48 (−1.97, 7.41)	6.8 (−5.4, 20.4)	0.31	1.13 (0.90, 1.45)
−4.76 (−11.95, 3.58)	−5.8 (−14.6, 4.4)	0.21	0.90 (0.78, 1.06)
1.64 (−0.91, 4.63)	7.1 (−4.0, 20.1)	0.18	1.20 (0.92, 1.59)
0.020 (−1.06[c], 1.68)	0.3 (−14.2[c], 22.6)	0.95	0.99 (0.73, 1.58)
−1.47 (−1.74[c], −0.19)	−15.4 (−17.8[c], −2.0)	0.012	0.73 (0.72[c], 0.89[c])

cave dose response for autoimmune hypothyroidism (*12*). However, no significant radiation risk was detected for other thyroid disease (*12*).

Thyroid abnormalities also occur after exposure to other sources of ionizing radiation, including external (*13*) and internal radiation (*14*). Although the prevalence of hypothyroidism or thyroiditis increased in patients who received radiation therapy (*15, 16*), the effects of relatively low doses of external radiation exposure are equivocal (*17*). The ongoing AHS thyroid study in Hiroshima and Nagasaki initiated in 2000 should help to examine radiation effects on specific thyroid diseases and to confirm the recent AHS findings for hypothyroidism and autoimmune thyroid disease (*12*).

Chronic Liver Disease and Cirrhosis

The significantly increased incidence of chronic liver disease and cirrhosis with radiation dose in the AHS is consistent with the LSS finding (*18*). In Japan, the predominant causes of chronic hepatitis and cirrhosis are HCV or HBV infection and excessive alcohol intake (*19*). The prevalence of anti-HBV surface antigen increased among the high-dose AHS subjects in 1975–1977 (*20*). Although the AHS study of anti-HCV antibody prevalence in 1993–1995 showed no dose response (overall prevalence was 9%), a possible radiation-associated increase in chronic liver diseases was found among anti-HCV antibody-positive individuals (*21*). The dose-related increase in the incidence of chronic liver disease and cirrhosis in our study might be partially explained by the persistent HBV infection or acceleration of active HCV infection among the heavily exposed survivors. On the other hand, an analysis of the risk factors for cirrhosis based on pathological review of about 1100 survivors who died between 1954–1997 did not show that A-bomb radiation increased the risk of liver cirrhosis (G. Sharp, personal communication). Additional studies including the measurement of HCV-RNA should help clarify the etiology of the dose-associated increase in chronic liver disease and cirrhosis. The dose response suggested in this report for fatty liver after 1986 should be confirmed in a more comprehensive future study that includes laboratory measurements such as of cholinesterase.

Uterine Myoma

Radiation risk for uterine myoma decreased with time since exposure. The higher radiation risk in the earlier follow-up period might be attributed to higher incidence in the older exposed female cohort, since uterine myoma is a hormone-dependent disease with peak incidence in the perimenopausal period.

To examine whether the significant radiation effects were due to bias from more frequent gynecological examinations of exposed women, especially early in the follow-up, a prevalence study of uterine nodules using ultrasonography was conducted during 1991–1993 in Hiroshima (*22*). That study demonstrated a significant dose–response relationship

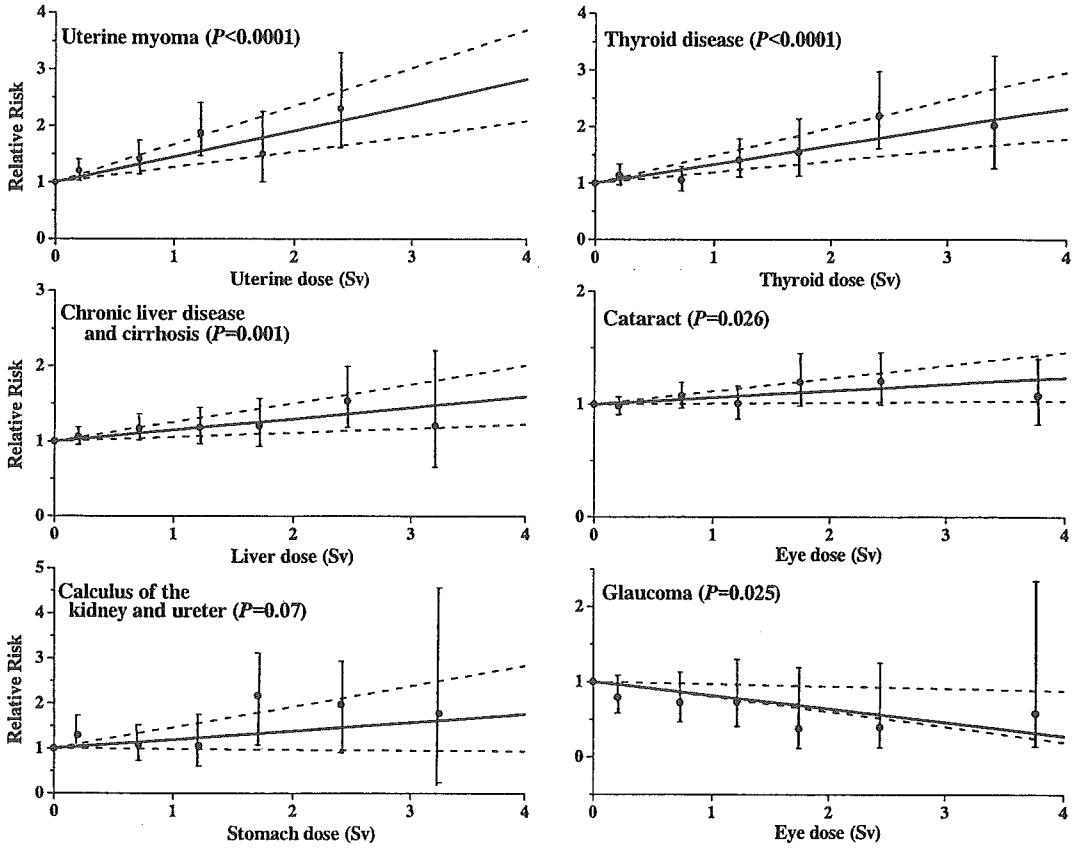

FIG. 1. Estimated linear dose response (solid line) for the incidence of six noncancer diseases with significant or suggestive radiation effects, 1958–1998. The 95% confidence bounds are shown as dotted lines. The estimated relative risks (●) and 95% confidence intervals are shown for each dose category.

(odds ratio estimate of 1.61 at 1 Sv), and the postulated bias was refuted.

The development of endometrial cancer or uterine sarcoma, but not benign nodules, many years after radiation therapy has been reported (*23, 24*). No significant risk for uterine carcinoma has been reported in the LSS (*25*). Since the pathogenesis of uterine myoma remains obscure, further studies are needed to elucidate the mechanism of the development of uterine myoma after A-bomb radiation exposure.

Cataracts

A previous AHS ophthalmological study revealed an increased prevalence of posterior subcapsular opacities in the high-dose group, especially among younger survivors (*26*), but an early AHS ophthalmological study (*27*) and our previous AHS noncancer incidence study for 1958–1986 (*1*) revealed no additional radiation effects on cataracts. However, 12 additional years of follow-up has revealed that the overall incidence of cataract was significantly increased with radiation dose. The cataract cases under 60 years of age at incidence in the most recent follow-up period may have enhanced detection of radiation effects. In recent studies, much-delayed lenticular changes were detected after radiotherapy (*28*), exposure to cosmic radiation among astronauts (*29*), and exposure from radiation-contaminated buildings in Taiwan (*30*). Our findings of a more elevated radiation risk for lens opacities among the younger participants and an increased RR with long latency are compatible with these findings (*28–30*).

Glaucoma

Glaucoma cases in this study were ascertained through self-reporting. Recent population surveys on glaucoma prevalence conducted in Singapore and the United States showed that prevalence rates were underestimated in the absence of detailed ophthalmological examination (*31, 32*). Since no other reports of a relationship between glaucoma and radiation were found in the literature, additional studies of cases ascertained through uniform application of tonometry and gonioscopy are warranted.

Hypertension

The incidence of hypertension increased with radiation dose, particularly for those with over 2 Sv of exposure. Although no human studies directly link radiation exposure with hypertension (*33*), radiation-induced nephropathy (*34*)

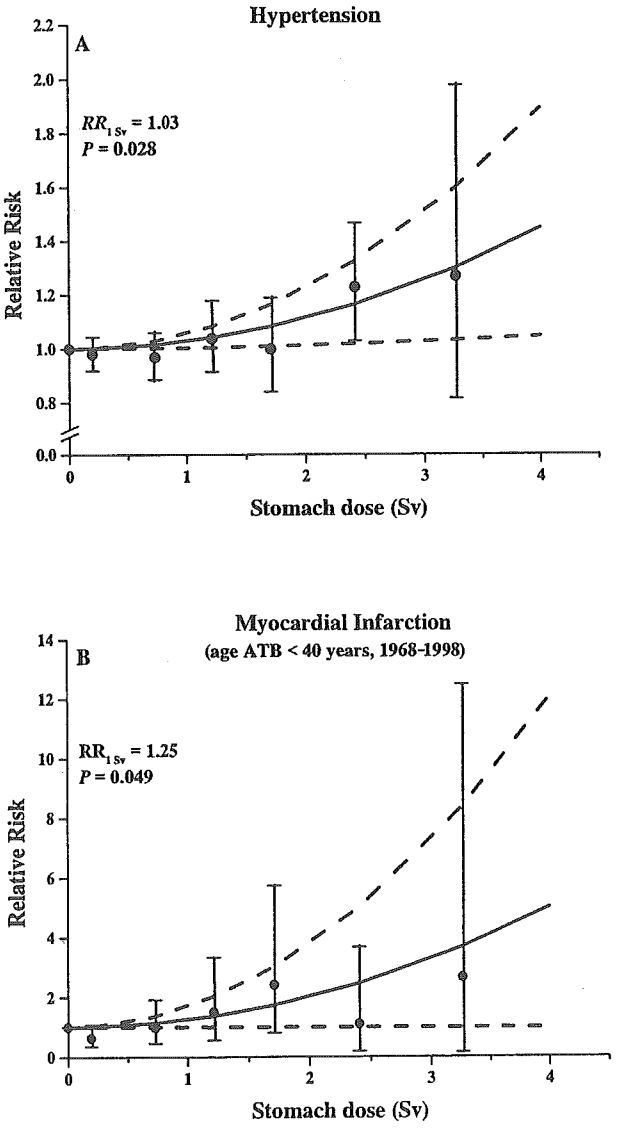

FIG. 2. Panel A: Estimated quadratic dose response for the incidence of essential hypertension, 1958–1998. Panel B: Estimated quadratic dose response for the incidence of myocardial infarction incident during 1968–1998 among AHS participants who were under 40 years ATB. The estimated relative risks (●) and the 95% confidence intervals are shown for each dose category.

and arterial hypertension (*35*) were reported, which may be relevant to current findings.

The AHS longitudinal analysis of blood pressure for 1958–1986 showed a small but statistically significant elevation in blood pressure levels in exposed survivors under 16 years of age (*36*). The trend, however, was reversed in the older cohort. Our present results are consistent with those of the longitudinal blood pressure trends for younger survivors. The discrepancy in the older cohort might be due in part to possible modification by medication and co-morbidity after the onset of hypertension.

Cardiovascular Disease

An increase in atherosclerosis and radiation-induced heart diseases has been reported in animal experiments and in humans after radiotherapy in the 1960s and 1970s and for occupational exposure before 1950 (*37–39*). Decreased risk of myocardial infarction by the use of modern techniques suggested that a relatively high dose of radiation may be involved in the induction of atherosclerotic lesions (*37, 40*).

An AHS longitudinal analysis of total serum cholesterol showed that the cholesterol levels of the irradiated subjects were significantly higher than those of the unirradiated subjects (*41*), and the same tendency was shown for the blood pressure trends among the younger cohort (*36*). These increases may partially explain the elevated incidence of myocardial infarction among the younger exposed subjects in this study.

One limitation of our study is that fatal MI and asymptomatic MI were not included. The ongoing AHS cardiovascular disease incidence study, which applies stringent criteria for case definition, including lethal heart attack cases, and measurements of atherosclerotic parameters such as carotid artery thickness, should provide additional information to improve our ability to elucidate the relationship between cardiovascular disease and radiation.

Calculus of the Kidney and Ureter

An increased risk with radiation dose was suggested for the first time for calculus of the kidney and ureter (P = 0.07), with the effects significantly evident for men. Although the prevalence of hyperparathyroidism (*42*) and the level of calcium (*43*) were increased with radiation dose in the AHS, the small number of hyperoparathyroid cases cannot fully explain the findings for nephrolithiasis. Also, the observed sex difference in radiation effects cannot be explained by calcium metabolism. The development of calculus of the kidney and ureter in the AHS participants merits further investigation.

In summary, this updated analysis examining the relationship between exposure to A-bomb radiation and the incidence of noncancer diseases between 1958 and 1998 showed a statistically significant linear positive dose–response relationship for thyroid disease, chronic liver disease and cirrhosis, and uterine myoma, which is consistent with our previous results (*1*). Our new findings include a positive linear dose–response relationship for cataract, a negative linear dose–response relationship for glaucoma, a quadratic dose–response relationship for hypertension and for MI in the younger cohort, and a suggested positive dose–response relationship for calculus of the kidney and ureter. In this study, we examined smoking and drinking as effect modifiers and found their effects to be minimal. Despite some limitations, such as restricted case ascertainment and necessary exclusion of nonparticipants, the results of this study offer important clues to the late effects of A-bomb radiation on the development of certain noncancer diseases.

TABLE 4
Estimated RR at 1 Sv (RR_{1Sv}) by Effect Modifiers for the Diseases with Evidence for Radiation Effects

Disease	Overall RR_{1Sv}	City			Sex			Age ATB (years)			
		Hiroshima	Nagasaki	*P*	Male	Female	*P*	10	25	40	*P*
Thyroid disease	1.33	1.40	1.25	0.31	1.26	1.35	0.61	1.64	1.15	1.03	0.0005
Liver disease	1.15	1.15	1.13	0.85	1.10	1.19	0.39	1.20	1.12	1.07	0.20
Uterine myoma	1.46	1.42	1.55	0.55	—	—	—	1.36	1.63	2.10	0.042
Cataract	1.06	1.05	1.10	0.47	1.11	1.04	0.24	1.12	1.07	1.04	0.29
Glaucoma	0.82	0.80	0.88	0.55	0.97	0.80	0.21	0.85	0.83	0.80	0.49
Calculus of the kidney and ureter	1.19	1.18	1.20	0.20[d]	1.47	0.86	0.007[d]	1.46	1.03	1.00	0.008[d]
Hypertension[b]	1.03	1.02	1.04	0.68	1.03	1.02	0.65	1.03	1.03	1.02	0.91
Myocardial infarction[c]	1.25	1.27	1.02	0.62	1.22	1.30	0.84	1.27	1.24	1.22	0.92

Disease	Overall RR_{1Sv}	Age at examination						Calendar time[a]				
		30	40	50	60	70	*P*	I	II	III	IV	*P*
Thyroid disease	1.33	1.88	1.53	1.32	1.19	1.12	0.002	1.50	1.23	1.24	1.57	0.36
Liver disease	1.15	1.26	1.21	1.16	1.13	1.10	0.25	1.05	1.15	1.24	1.10	0.60
Uterine myoma	1.46	1.57	1.50	1.44	1.38	1.34	0.72	2.00	1.71	1.10	1.32	0.015
Cataract	1.06	2.09	1.67	1.21	1.07	1.02	0.0005	1.17	1.04	1.00	1.08	0.086
Glaucoma	0.82	0.92	0.90	0.88	0.85	0.82	0.41	0.80	0.90	0.83	0.85	0.88
Calculus of the kidney and ureter	1.19	2.30	1.53	1.21	1.09	1.04	0.019	0.72	1.09	1.31	1.29	0.13[e]
Hypertension[b]	1.03	1.04	1.04	1.03	1.02	1.02	0.59	1.02	1.03	1.04	1.00	0.71
Myocardial infarction[c]	1.25	2.56	1.83	1.44	1.24	1.12	0.37	—	1.36	1.31	1.12	0.78

Note. Background stratified by city, sex, age ATB, age ATE, and calendar time.
[a] Calendar time: July 1958–June 1968 (I), July 1968–June 1978 (II), July 1978–June 1988 (III), July 1988–June 1998 (IV).
[b] Based on the quadratic dose–response model.
[c] Based on the quadratic dose–response model, for incidence during 1968–1998 and age ATB under 40 years.
[d] χ^2 $df = 2$ test.
[e] χ^2 $df = 4$ test.

APPENDIX
Twenty-one Noncancer Diseases and their International Classification of Disease (ICD) Codes over Time

Disease	ICD edition		
	7th	8th	9th
Hypertension	444, 445	400, 401	401
Hypertensive heart disease	440–443	402, 404	402, 404
Ischemic heart disease	420	410–414	410–414
Myocardial infarction	—	410	410
Occlusion, stenosis	332	433, 434	433, 434
Aortic aneurysm	451, 452	441, 442	441, 442
Stroke I	330–332	430, 431, 433, 434	430, 431, 433, 434
Stroke II	330–332, 334	430, 431, 433, 434, 436	430, 431, 433, 434, 436
Thyroid diseases	250–254	240–245	226, 240–245
Cataract	385	374	366
Gastric ulcer	540	531	531
Duodenal ulcer	541	532	532
Chronic liver disease and cirrhosis	581, 583	571, 573	571
Cholelithiasis	584	574	574
Calculus of kidney and ureter	602	592	592
Uterine myoma	214	218	218
Cervical polyp	215	219	216, 622
Hyperplasia of prostate	610	600	600
Dementia	304, 305	290	290
Parkinson's disease	350	342	332
Glaucoma	387	375	365

Note. Myocardial infarction was identified after June 1964.

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Cataract in atomic bomb survivors

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Abstract.
Purpose: Ophthalmologic examinations were conducted on atomic bomb (A-bomb) survivors 55 years after exposure.
Materials and methods: A-bomb survivors who had been exposed before 13 years of age at the time of the bombings in 1945 or who had been examined in a previous study between 1978 and 1980. The examinations, conducted between June 2000 and September 2002, included slit-lamp examination, digital photography and a cataract grading system for three parts of the lens (nucleus, cortex and posterior subcapsule) as an outcome variable. Proportional odds logistic regression analysis was conducted using the lowest grading class as a reference and included explanatory variables such as age, sex, city, dose and various cataract-related risk factors. When the grades in an individual differed, the worst grade was used.
Results: Results indicate that odds ratios (ORs) at 1 Sv were 1.07 (95% confidence intervals [CI] 0.90, 1.27) in nuclear colour, 1.12 (95% CI 0.94, 1.30) in nuclear cataract, 1.29 (95% CI 1.12, 1.49) in cortical cataract and 1.41 (95% CI 1.21, 1.64) in posterior subcapsular cataract. The same was true after excluding 13 people whose posterior subcapsular cataracts had been previously detected.
Conclusion: Significant radiation effects were observed in two types of cataracts in A-bomb survivors.

1. Introduction

The eye lens is in the anterior part of the eye in a capsule consisting of non-nucleated lens fibre cells forming the lens nucleus and cortex (outer layer), and one layer of nucleated epithelial cells covering the surface of the lens (Masuda 1993). It is one of the most radiosensitive organs in both humans and animals because epithelial cells at the equator (located in the rim portion of the lens) proliferate and continue moving towards the centre of the lens for the entire life of the organism. While moving toward the centre of the lens, the epithelial cells are stretched, squeezed and lose nuclei, resulting in fibre cells. The fibre cells contain specific proteins called crystallins that keep the lens transparent by chaperon activity. Cataract pathogenesis, induced by a variety of insults such as ultraviolet light, is impairment of epithelial cell proliferation and/or oxidative degeneration of lens fibre proteins. Impaired epithelial cells let water and minerals into the lens; healthy cells keep them out by active transport. Pathogenic changes of the lens are clinically observed as opacities (opaque change). Visual acuity is usually not impaired by the opacities if they have not advanced to the central part (visual axis) of the lens.

Previous ophthalmological studies conducted among atomic (A) bomb survivors provide important evidence of the stochastic effect of radiation (Miller *et al.* 1969, Choshi *et al.* 1983). Radiation-induced cataract develops relatively early (6 months to 2 years) among the late effects of radiation (Miller *et al.* 1969, Choshi *et al.* 1983). Infants who receive radiotherapy (1–8 Gy) for haemangioma, however, develop posterior subcapsular or cortical opacities in the untreated eyes 30–45 years later, and defective lens fibre formation can continue, probably because of a clone of damaged germinal epithelial cells (Wilde and Sjöstrand 1997). Children exposed to a lenticular dose of 1 Gy have a 50% increased risk (OR 1.50; 95% confidence interval [CI] 1.10–2.05) of developing a posterior subcapsular opacity and a 35% increased risk of developing a cortical opacity (OR 1.35; 95% CI 1.07–1.69) (Hall *et al.* 1999), indicating early onset cortical opacities.

The relationship between these types of lens changes and radiation dose in A-bomb survivors exposed in their youth was studied in the present paper. To assess precise radiation effects, two systems were used. First, to grade different degrees of opacities (opaqueness) in nuclear (central part of the lens), cortical (outer layer of the lens) and posterior subcapsular cataracts (rear portion of the lens and underneath the lens capsule), the Lens Opacity

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Classification System (LOCS) II was used, in which standard pictures of nuclear (opalescence and colour), cortical (five standards) and subcapsular cataracts (four standards) were employed. The system shows good inter- and intra-observer reproducibility (Chylack *et al.* 1989). LOCS II enabled assessment of quantitative lens changes not previously studied in A-bomb survivors. Second, to assess the effect of various cataract risk factors on radiation-induced cataract, 17 ophthalmological findings, 23 host and environmental factors, 15 laboratory tests for potentially relevant conditions, i.e. diabetes mellitus, cardiovascular disease, obesity (Klein *et al.* 1998, Hutnik *et al.* 1999, Leske *et al.* 1999), steroid medications (Cumming and Mitchell 1998), ultraviolet light exposure (Katoh *et al.* 1997, Cruickshanks 1998, Hayashi *et al.* 1998), inflammation (Schaumberg *et al.* 1999), calcium level (Srivastava and Srivastava 1989), and smoking (Hiller *et al.* 1997) were tested. We then searched for 'intermediate risk factors', to which radiation causes some alterations that in turn cause lens opacities.

2. Materials and methods

2.1. *Subjects*

Subjects were part of the Adult Health Study (AHS) conducted in Hiroshima and Nagasaki who have undergone biennial examinations since 1958. Two groups, those undergoing ophthalmological examinations in the previous study (1978–80) and who satisfied the study requirements, as well as those who were less than 13 years old at the time of the bombings were eligible for study. Among the 2042 people who underwent ophthalmological examination in the previous studies, 1284 were alive at September 1999. Among those who were 13 years old or less at the time of the bombings, 2774 were alive at September 1999. Of those, 913 agreed to participate in the study initially and again at the time of their visits. All were given a full explanation of the procedures and the possible adverse effects of the mydriatics (0.5% tropicamide and 0.5% phenylephrine hydrochloride) that would be administered. The Human Investigation Committee at the Radiation Effects Research Institute (RERF) approved the study protocol.

2.2. *Study methods*

2.2.1. *Ophthalmologic examinations.* Ophthalmological examinations were conducted one or two mornings a week at the RERF during the study period by ophthalmologists from Hiroshima or Nagasaki universities. Comprehensive examinations for the function and structure of the eye, including visual acuity, intra-ocular pressure, refraction, and pictures of various parts of the eye with ophthalmological apparatuses, were conducted. For those with signs of serious disease, careful medical procedures were taken.

Specifically, the following nine ophthalmological examinations were conducted: (1) questionnaire; (2) objective refractory examination with an autorefractometer (RM-8000, Tokyo, Japan); (3) corrected visual acuity test with a 5-metre acuity chart; (4) intra-ocular pressure measurement with an applanation tonometer; (5) anterior chamber examination with a slit-lamp biomicroscope (chamber angle with gonioscopy, if necessary); (6) lens examination with a slit-lamp biomicroscope; (7) lens photographs; (8) posterior retina examination with an indirect ophthalmoscope and a slit-lamp biomicroscope; and (9) retro-illumination examination of the lens with a fundus camera and a slit-lamp biomicroscope. Examinations 1–5 were conducted on all participants. When a narrow anterior chamber angle was detected, a further examination under mydriasis was not performed. When a normal anterior chamber angle was detected, mydriatics were instilled, we waited for 30 min and then conducted examinations 6–9. After examination, a miotic (1% pilocarpine hydrochloride) was instilled. Digital images of the lens were stored in a computer (ImageNet®, Topcon).

2.2.2. *LOCS II classification.* Ophthalmologists made diagnoses using lens photographs and coded them according to LOCS II, in which standard pictures of nuclear (opalescence and colour), cortical (five standards) and subcapsular cataracts (four standards) were used. The classification system provides good inter- and intra-observer reproducibility (Chylack *et al.* 1989). Diagnostic standardization was conducted every 6 months, and agreement among the ophthalmologists in Hiroshima and Nagasaki was consistently over 80%.

2.2.3. *Medical questionnaire and clinical laboratory tests.* Information about ocular diseases, eye surgery, past and present systemic diseases that might have induced lens opacities, duration of exposure to ultraviolet light during outdoor work and leisure activities, and radio- and/or chemotherapy history were obtained by interview. Clinical laboratory tests related to cataract development among the AHS examinations, such as white blood cell count, erythrocyte sedimentation rate, alpha 1 globulin, alpha 2 globulin, calcium, phosphorus, glucose, and haemoglobin A1C (HbA1C) were incorporated into the analysis.

2.3. *Statistical methods*

Findings from the worse eye were used to produce a univariate outcome from bivariate outcomes of the right and left eyes. In the current study, outcomes were binary or ordered polytomous. To estimate outcome prevalences, we applied a logistic regression model to the binary outcome the proportional odds regression model to ordered polytomous data which is a standard model for ordered polytomous data like ophthalmological changes. The fitted model was as follows:

$$\log\left[\frac{\gamma_j}{1-\gamma_j}\right]=\theta_j+\beta_C C+\beta_S S+\beta_B(\text{ageATB}-5)/10+\beta_D D,$$

where $\gamma_j=\Pr(Y\geqslant j)$ for $j=1, \ldots, R$ and Y is an $(R+1)$-ordered polytomous outcome that takes a value in $\{0, 1, \ldots, R\}$, θ_j's are cut points, C is the city indicator (0=Hiroshima, 1=Nagasaki), S is a sex indicator (0=male, 1=female) and D is DS86 eye dose (Sv) for those older than 0 years at the time of the bombings and DS 86 mother's uterus dose for those in gestation, with relative biological effects (RBE) for a neutron being 10. Age ATB is age at the time of bombings. Gamma and neutron eye doses were truncated at 4 Gy in a total Kerma dose. The meaning of β_D in the proportional odds model above is the log OR per Sv in the logistic model for new binary outcomes produced from the ordered polytomous data in the way that the new binary response is 1 for $Y\geqslant j$ and 0 for $Y<j$ using cut-off category level j. When slopes are defined in this way, the slope parameter β_D is generally dependent on the cut-off category level. However, the proportional odds model assumes the β's to be common, and the common parameter is estimated by an iterative multivariate least-squares method (McCullagh and Nelder 1989).

Inflammation-related variables (white blood cell count, alpha 1 globulins, alpha 2 globulins, and erythrocyte sedimentation rate) were summarized by principal component analysis. The first principal component score (size factor) that was adjusted to the variance equal to 1 was used for an explanatory variable in the regression analysis for posterior subcapsular opacity in the Results. All computations were done with a STATA 8.0 statistical package.

3. Results

The study was conducted between June 2000 and September 2002. Total examinees numbered 913 (table 1). A slit-lamp examination was not conduct on 30 people because of contraindication or refusal. Among the 883 people examined, six had undergone surgery in both lenses and four had received unknown radiation doses. Therefore, 873 people were included in the analysis. Among them, a lens was present in only the right eye in 15 people, in only the left in 21, and in both in 827. Among those with lenses in both eyes, the worse finding was used for analysis. The distribution of examinees by A-bomb radiation dose and age at exposure is shown in table 2. Of the 873 subjects, 533 were in Hiroshima at the time of the bombings and 340 were in Nagasaki. Age at the time of the bombings ranged from −0.8 to 37.9 years (mean 8.8 years). Age at the time of the examination ranged from 54.3 to 94.4 years (mean 64.8 years). The subjects comprised 344 men and 529 women. The participation rate stratified by radiation dose groups did not vary with radiation dose.

Table 3 shows the distribution of cases by LOCS II classification. Regression analysis with the proportional odds model which used the lowest group as a reference revealed that ORs at 1 Sv were 1.07 (95% CI 0.90, 1.27) in nuclear colour, 1.12 (95% CI 0.94, 1.30) in nuclear opacities, 1.29 (95% CI 1.12, 1.49) in cortical opacities, and 1.41 (95% CI 1.21, 1.64) in posterior subcapsular opacities (table 4 and figure 1). The same was true after removing 13 people who had

Table 1. Profile of examinees in the ophthalmological study of A-bomb survivors during 2000–02.

All examinees	913
No slit-lamp examination	30
Instillation refusal	6
Contraindication	24
Slit-lamp examination	883
Postoperative state	6
Dose unknown	4
Single eye, right	15
Single eye, left	21
Both eyes	837

Values are numbers (*n*).

Table 2. Age of subjects at the time of the bombings, and radiation dose.

	Age (years)			
Dose (Sv)	*In utero*	0–13	>13	Total
<0.005	87	233	131	451
0.005 to <0.5	50	129	11	190
0.5 to <1.0	4	59	28	91
1.0 to <2.0	1	48	40	89
2.0	1	32	19	52
Total	143	501	229	873

Participation rate stratified by radiation dose groups did not vary with radiation dose.

Table 3. Distribution of cases by Lens Opacity Classification System (LOCS) II grade ($n=873$).

	LOCS II grade						
	0	1	2	3	4	5	6
Nuclear colour	528	297	48				
Nuclear opacity	322	441	85	21	4		
Cortical opacity	111	289	153	164	110	43	3
Posterior subcapsular opacity	631	178	49	10	5		

The LOCS II grades different degrees of opacities (opaqueness) in nuclear (central part of the lens), cortical (outer layer of the lens) and posterior subcapsular cataracts (rear portion of the lens and underneath the lens capsule) by using standard pictures.

posterior subcapsular opacities during the previous study. After adjusting for city, sex, age at the time of the bombings and smoking, significant dose–effects were found for diabetic retinopathy, retinal arteriolosclerosis and retinal degeneration, ORs being 1.71 (95% CI 1.25, 3.33), 1.58 (95% CI 1.26, 1.97), and 1.42 (95% CI 1.07, 1.86), respectively (table 4). The prevalence of cortical opacities was significantly higher in women, the elderly and Nagasaki residents than in men, the young and Hiroshima residents. Posterior subcapsular opacities were significantly more prevalent in the elderly than in the young but were not associated with city or sex (table 5). Cortical and posterior subcapsular opacities were significantly correlated each other ($r=0.333$, $p<0.001$).

Among the 23 questionnaire items and 15 laboratory findings that are reportedly risk factors for lens opacities, significant association with radiation dose was found for smoking, white blood cell count, alpha 1 globulin, alpha 2 globulin, erythrocyte sedimentation rate, calcium, glucose and HbA1C. Among the above radiation-associated factors, factors in turn associated with lens opacities or intermediate risk factors were further tested and significant association with posterior subcapsular opacities was found in white blood cell counts, serum calcium levels and HbA1C, and suggestive association with cortical opacities was found in retinal arteriolosclerosis and alpha 1 globulin. Only smoking was a potential confounding factor, but it was not significant risk factor. Regression analysis with the proportional odds model that included those intermediate risk factors

Table 4. Odds ratios of ophthalmological findings at 1 Sv adjusting for city, sex, age at the time of the bombings and smoking.

Item	Odds ratio	95% Confidence interval
Lens Opacity Classification System II:		
Nuclear colour	1.07	0.90, 1.27
Nuclear opacity	1.12	0.94, 1.30
Cortical opacity	1.29	1.12, 1.49
Posterior subcapsular opacity	1.41	1.21, 1.64
Other ophthalmological findings:		
Visual acuity (log MAR)	0.005*	−0.006, 0.017
Intra-ocular pressure (mmHg)	0.088*	−0.127, 0.303
Abnormality in eyelid ($n=38$)	1.01	0.66, 1.53
Conjunctiva ($n=26$)	0.91	0.53, 1.59
Refraction (diopter) (axis)	−1.417*	−4.602, 1.767
Abnormality in cornea ($n=93$)	1.24	0.99, 1.55
Abnormality in anterior chamber ($n=41$)	1.24	0.92, 1.68
Abnormality in iris ($n=24$)	1.09	0.72, 1.64
Abnormality in pupil ($n=28$)	1.11	0.75, 1.65
Abnormality in light reflex direct ($n=12$)	0.29	0.05, 1.70
Abnormality in light reflex indirect ($n=10$)	0.89	0.40, 2.01
Abnormality in macula ($n=92$)	1.06	0.83, 1.35
Papilla atrophy ($n=51$)	1.18	0.89, 1.58
Diabetic retinopathy ($n=20$)	1.71	1.26, 2.33
Retinal arteriolosclerosis ($n=84$)	1.58	1.26, 1.97
($n=69$)**	1.49	1.15, 1.94
Retinal degeneration ($n=55$)	1.42	1.07, 1.88
($n=41$)***	1.42	1.00, 2.02
Retinal atrophy ($n=27$)	1.26	0.90, 1.77
($n=22$)***	1.49	1.04, 2.14

*Coefficient for continuous variables.
**Diabetic retinopathy excluded.
***Diabetic retinopathy and arteriolosclerosis excluded.