



Relationship Between Radiation Exposure and Incident Atrial Fibrillation Among Atomic Bomb Survivors

Daisuke Haruta, MD, PhD; Reid D. Landes, PhD; Ayumi Hida, MD, PhD;
Misa Imaizumi, MD, PhD; Waka Ohishi, MD, PhD;
Masazumi Akahoshi, MD, PhD; Koji Maemura, MD, PhD

Background: Atrial fibrillation (AF) is a common arrhythmia. Although radiation exposure is associated with an elevated risk of cardiovascular disease, the effects of radiation on arrhythmia, especially AF, are unclear. We evaluated the relationship between radiation and AF in a cohort of atomic bomb survivors.

Methods and Results: From a baseline enrollment period (1967–1969) to 2009, 7,379 Hiroshima and Nagasaki atomic bomb survivors (mean baseline age 50.6 years, 65.8% women, 72.9% from Hiroshima) without AF and who had been exposed to estimated radiation doses between 0 and 3.614 Gy were followed-up once every 2 years. AF was identified by 12-lead electrocardiograms and medical records. Treating age as the time scale, AF incidence was modeled with Cox proportional hazards models adjusting for demographics, AF risk factors, and radiation. We modeled radiation as both a continuous variable and categorized according to radiation dose (Control [<0.005 Gy] and 5 equal-sized groups based on radiation dose quintiles in the cohort). Over 4 decades of follow-up, we identified 276 AF cases in 176,687 person-years, for an incidence rate of 1.56 per 1,000 person-years. After adjusting for sex and city, neither categorized, linear, nor linear-quadratic models showed substantive evidence of radiation effects. Similar results were obtained after adjusting for AF risk factors.

Conclusions: There were no clear positive associations between radiation dose and AF risk, rather null or non-significant inverse associations.

Key Words: Atrial fibrillation; Incidence; Radiation

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. The prevalence and incidence of AF increase with age.^{1–3} AF is associated with an increased risk of ischemic stroke, congestive heart failure, reduced quality of life, and mortality.^{4–6} AF is a multifactorial disease affected by both environmental and genetic factors.⁷ Past studies have established various risk factors for AF, such as aging, male sex, hypertension, obesity, diabetes, hyperthyroidism, alcohol consumption, smoking tobacco, hyperuricemia, and organic heart diseases.^{7–9} As possible underlying pathways, there is emerging evidence linking inflammation and oxidative stress to the pathogenesis of AF through atrial fibrosis and electrical and structural remodeling.^{10–12}

The use of ionizing radiation for diagnostic and thera-

peutic purposes has increased worldwide. Recently, several studies reported that moderate to high doses (0.5–20 Gy) of radiation exposure were associated with an increased risk of cardiovascular diseases, such as ischemic heart disease, congestive heart disease, rheumatic valvular disease, and hypertensive heart disease.^{13–15} With regard to radiation-associated conducting system abnormalities and arrhythmias, there are case reports of advanced sick sinus syndrome, atrioventricular block, and bundle branch block long after radiotherapy with high doses >30 Gy.¹⁶ Of 48 Hodgkin disease survivors who received mediastinal irradiation (27–52 Gy), 74.5% had conduction abnormalities or arrhythmia on resting electrocardiograms (ECGs) 6–27 years after irradiation.¹⁷ A recent report found that among cancer patients, the prevalence of AF was higher

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Department of Clinical Studies, Radiation Effects Research Foundation, Nagasaki and Hiroshima (D.H., A.H., M.I., W.O., M.A.); Saikakai Shibata Chokodo Hospital, Shimabara (D.H.); Department of Statistics, Radiation Effects Research Foundation, Hiroshima (R.D.L.), Japan; Department of Biostatistics, University of Arkansas for Medical Sciences, Little Rock, AR (R.D.L.), USA; Wakokai Keiju Hospital, Isahaya (M.A.); and Department of Cardiovascular Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki (K.M.), Japan

K.M. is a member of *Circulation Reports*' Editorial Team.

Mailing address: Ayumi Hida, MD, PhD, Department of Clinical Studies, Radiation Effects Research Foundation, 1-8-6 Nakagawa, Nagasaki 850-0013, Japan. E-mail: ayumih@rerf.or.jp

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among those receiving radiation therapy (doses were not reported).¹⁸ For a low to moderate range of radiation (not exceeding 4 Gy), we have examined radiation-associated risks of Brugada-type ECG,¹⁹ early repolarization,²⁰ and complete right bundle branch block²¹ among atomic bomb survivors, but found no evidence of altered risk.

Although occupational radiation exposure is limited to low doses by regulations, some radiologists and cardiologists who are engaged in interventional medical procedures are repeatedly exposed to low doses of radiation.²² The association between low-dose radiation and AF has not been clarified, and several lines of evidence support a significant association between atomic bomb radiation and AF risk factors such as high blood pressure,²³ heart diseases,¹³ enhanced inflammation, and oxidative stress.^{24,25} Thus, the aim of the present study was to evaluate the effects of radiation on the incidence of AF over a low to moderate range of radiation doses, while accounting for risk factors such as smoking tobacco, drinking alcohol, body mass index (BMI), hypertension, hypercholesterolemia, hyperuricemia, and heart disease, among Hiroshima and Nagasaki atomic bomb survivors over 4 decades of follow-up.

Methods

General Procedures and Study Design

In all, 19,961 participants have been followed-up once every 2 years in Hiroshima and Nagasaki since 1958 as part of a follow-up program of atomic bomb survivors of the Radiation Effects Research Foundation (RERF).²⁶ The follow-up health examinations of the atomic bomb survivors consisted of history taking, a physical checkup, and blood tests. Trained nurses collected information about past and present histories of physician-diagnosed diseases, including AF. Standing height and body weight were measured without socks or outer clothing. Blood pressure was measured with a mercury sphygmomanometer after a sufficient sedentary period. Total cholesterol and uric acid were measured with an AutoAnalyzer (Technicon Instrument) in the Hiroshima laboratory. A resting standard 12-lead ECG was obtained by regular procedures. Clinical and ECG diagnoses have been stored in databases using the 7th, 8th, 9th, and 10th editions of the International Classifications of Disease (ICD-7, -8, -9, and -10, respectively) and the modified Minnesota codes (Kagan-Yano code used by the RERF), respectively. The ICD database was started at the beginning of the health examination program, but the ECG database was not started until July 1967. Information regarding cigarette smoking and alcohol consumption was obtained from several mail surveys and interviews at the examinations.

The 2-year period from July 1, 1967 to June 30, 1969 was considered as the baseline for the present study. Of the 11,250 participants (64.3% women) examined at baseline, 29 with existing AF and an additional 3,842 without estimated radiation doses were excluded. The remaining 7,379 participants (65.8% women) were included in the present analyses. Follow-up in this study for each participant was defined as the period from baseline to either the first detection of AF, the last AF-free examination date, or December 31, 2009.

Informed consent was obtained from all participants. The Research Protocol Review and Human Investigation Committees of the RERF approved the study protocol (RP A1-15).

Definition of Incident AF

AF cases were identified by ECG recordings and medical diagnosis (ICD-7, -8, -9, and -10 codes 433.1, 427.9, 427.3, and I48, respectively). A cardiologist (D.H.) ascertained whether there was electrocardiographic evidence of AF or whether a medical report clearly indicated a history of AF for each incident or prevalent AF case. The examination date when AF was first recognized by ECG or medical diagnosis at the RERF was defined as the date of AF diagnosis.

Risk Factors

Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or medication with antihypertensive agents. Hypercholesterolemia was defined as total cholesterol ≥ 5.7 mmol/L or medication with lipid-lowering agents. Hyperuricemia was defined as serum uric acid ≥ 416 μ mol/L or an apparent history of gout or hyperuricemia with or without treatment. BMI was calculated by dividing body weight (kg) by the square of standing height (m²). Smoking tobacco and alcohol habits were categorized as ever (current or past) or never smoker or drinker, respectively. Heart disease was defined as having a history of valvular heart disease (ICD-7 codes 410–413, 421; ICD-8 codes 394–397), hypertrophic or dilated cardiomyopathy (ICD-7 code 422; ICD-8 codes 422, 425), congestive heart failure (ICD-7 code 422; ICD-8 codes 422, 425), or ischemic heart disease (ICD-7 code 420; ICD-8 codes 410–414). Information on risk factors was obtained from the clinical diagnosis and laboratory databases. Biochemical values have been standardized. All risk factors were prevalent events evaluated at baseline for each individual.

Radiation Dose

The current dosimetry system, Dosimetry System 2002 (DS02),²⁷ was used to estimate the stomach atomic bomb radiation dose of individuals as a surrogate for the heart dose, as described previously.²⁸ The radiation dose in weighted Gy equivalents was calculated using a relative biological effectiveness of 10 for neutrons; thus, the dose was the sum of the gamma dose and 10 times the neutron dose.²⁹

Statistical Analysis

Participant Characteristics Of the 7,379 participants, 2,878 made up the control group (radiation dose < 0.005 Gy). The remaining 4,501 participants (radiation dose ≥ 0.005 Gy) were divided into 5 radiation groups of approximately 900 people in each (Groups I–V; **Table 1**). Thus, there were 6 radiation dose groups. **Table 1** provides the mean radiation dose for each of the groups. Baseline characteristics and cofactors were compared among the 6 radiation groups using χ^2 tests for differences in proportions and *F*-tests for differences among means.

AF Risk Models AF incidence was modeled on the interval (start age, end age) with Cox proportional hazards regression.³⁰ All models included city and sex (the base model). With the significance level set at 0.05, we individually tested the contribution of each possible AF risk factor (BMI, alcohol consumption, smoking status, hypertension, hypercholesterolemia, hyperuricemia, and underlying heart disease). All significant risk factors were added to the base model. Those risk factors that were no longer significant were then dropped from the base model, thus arriving

Table 1. Participant Characteristics at Baseline Overall and According to Radiation Dose Category

	Overall (n=7,379)	Radiation dose category						P value
		Control (n=2,878)	Group I (n=900)	Group II (n=900)	Group III (n=900)	Group IV (n=901)	Group V (n=900)	
Stomach dose (Gy)								–
Mean	0.378	0.001	0.065	0.185	0.385	0.755	1.709	
Range	0.000–3.615	0.000–0.005	0.005–0.115	0.115–0.272	0.272–0.531	0.531–1.013	1.013–3.615	
Sum of person-years	176,687	70,210	21,789	20,738	20,440	21,971	21,539	–
From Hiroshima (%)	72.9	69.3	85.2	81.8	82.0	62.6	64.6	<0.001 ^C
Female sex (%)	65.8	64.4	68.9	71.6	68.2	64.7	60.7	<0.001 ^C
Age (years)								
At the time of the bombings	27.7±13.9	27.6±13.9	28.0±14.2	29.9±14.1	29.5±13.5	26.9±13.1	24.7±13.9	<0.001 ^D
At study start	50.6±13.9	50.5±13.9	50.9±14.2	52.7±14.1	52.4±13.5	49.8±13.1	47.6±13.9	<0.001 ^D
Follow-up duration (years)	23.9±13.4	24.4±13.4	24.2±13.6	23.0±13.1	22.7±13.2	24.4±13.5	23.9±13.2	0.006 ^D
Death in 2-year interim (%)	37.6	36.3	34.1	37.6	40.4	37.5	42.4	0.002 ^C
Hypertension ^A (%)	33.4	31.9	33.7	37.6	36.7	35.4	28.3	<0.001
Hypercholesterolemia ^A (%)	15.0	13.4	16.6	17.9	16.4	15.8	13.1	0.003
Hyperuricemia ^A (%)	6.1	6.7	5.2	4.7	5.1	6.0	7.2	0.079
Heart disease ^A (%)	0.7	0.8	0.6	0.7	0.4	0.7	1.0	0.728
Alcohol drinker ^A (%)	37.3	36.8	37.6	32.8	38.6	36.1	42.9	<0.001
Smoker ^A (%)	41.6	41.0	39.7	39.3	41.8	41.9	47.5	0.006 ^C
Body mass index ^A	21.8±3.3	21.8±3.3	22.0±3.2	22.0±3.4	21.6±3.2	21.9±3.5	21.8±3.2	0.247 ^D
Atrial fibrillation ^B (%)	3.7	3.7	3.8	4.8	4.3	3.4	2.6	0.197 ^C

Unless indicated otherwise, values are the mean ± SD. Data for alcohol drinking, smoking, and body mass index were not available for 277, 130, and 231 participants, respectively; the denominators were reduced from 7,379 accordingly. "Death in 2-year interim" refers to the percentage of participants who died within the 2 years since their last visit. ^AAt the first examination (baseline). ^BAt the last observation. ^CDetermined using a χ^2 test. ^DDetermined using an $F_{5,7147}$ test.

at the adjusted model, which included city, sex, BMI, underlying heart disease, and hypercholesterolemia.

In both the base and adjusted models, we evaluated radiation effects when radiation dose was considered as a continuous variable (primary results) and when categorized into 6 radiation groups (secondary results). For the primary results, we modeled radiation as a linear quadratic. We also individually evaluated whether any of the significant risk factors interacted with radiation dose, but none did. We report hazard ratios (HRs); their 95% confidence intervals (CIs) and P values were based on profile log-likelihood functions. The significance level was two-tailed, set at 0.05.

Power Considerations Others have observed overall AF incidence rates between 2 and 6 per 1,000 person-years;^{31–33} these rates were observed in cohorts (none of which were exposed to radiation) with mean ages at baseline between 5 and 9 years older than the present cohort. Assuming an incidence rate of 6 per 1,000 person-years in those not exposed to radiation, the Cox proportional hazards model proposed above would have at least 0.80 power to detect an HR of 1.15 (log-linear slope of 0.140) for 1-Gy exposure using a 0.05 significance level test with our cohort. If the non-exposed incidence rate was as low as 1 per 1,000 person-years, the detectable HR would be 1.40 (log-linear slope of 0.336). These effect size calculations were estimated with simulation using our cohort's ages and radiation exposures, and assumed other factors (e.g., sex, city) were independent of radiation exposure level.

All analyses described above, including simulations for power considerations, were conducted using SAS/STAT version 9.3 (SAS System for Windows; SAS Institute, Cary, NC, USA).

Results

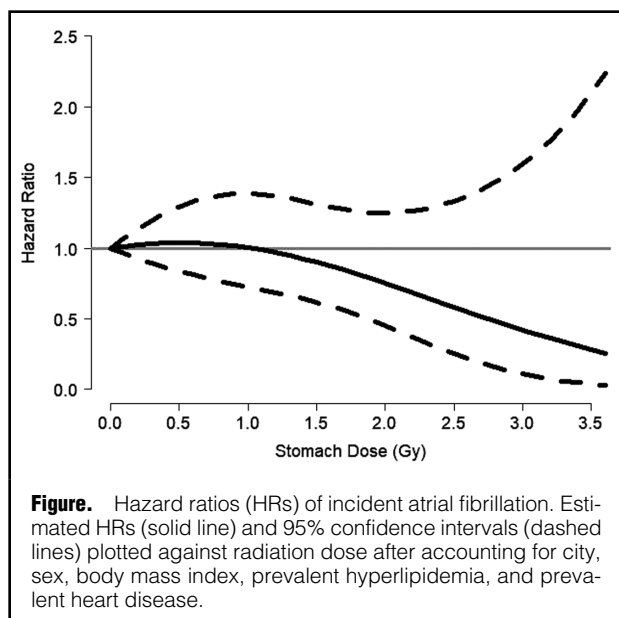
Baseline Characteristics

Of 7,379 participants, 4,859 (65.8%) were female and 5,381 (72.9%) were from Hiroshima. The mean age at baseline was 50.6 years (range 22–90 years). The mean stomach weighted dose was 0.378 Gy (range 0–3.614 Gy). Between 1969 and 2009, there were 176,687 person-years accumulated, and 276 incident AF cases (151 in women) were identified, of which 262 were determined by ECG in the RERF examination once every 2 years. Thus, the incidence rate was 1.56 per 1,000 person-years overall, with the incidence rate in females and males separately being 1.25 and 2.25 per 1,000 person-years, respectively. Age-stratified incidence rates were 0.51, 1.47, 2.93, and 4.97 per 1,000 person-years for those aged 50–59, 60–69, 70–79, and ≥80 years, respectively.

Table 1 shows the characteristics of the study sample overall and in each of the 6 radiation dose categories (Control and Groups I–V). The radiation dose groups differed in the proportion of participants from Hiroshima ($\chi^2=241.7$, $P<0.001$) and female participants ($\chi^2=33.13$, $P<0.001$), with a tendency for those in the middle radiation groups (Groups I, II, and III) to be more likely from Hiroshima and female than those in the Control group and higher radiation groups (Groups IV and V). Age at the time of bombing also differed among the radiation dose groups, with those in the middle radiation groups tending to be older than those in the 2 highest radiation groups ($F_{5,7373}=16.72$, $P<0.001$). Age at study start and years of follow-up reflected the difference in age at the time of bombing, with those in the middle radiation dose groups tending to be followed for less time than those in the lower and upper radiation dose groups. Two characteristics that showed an increas-

Table 2. HRs and 95% CIs for Atrial Fibrillation Risk Factors in the Base Model ^A		
Single risk factor	HR (95% CI)	P value
Heart disease	9.91 (5.41–18.18)	<0.001
Body mass index	1.09 (1.05–1.12)	<0.001
Hypercholesterolemia	0.67 (0.46–0.99)	0.046
Hypertension	1.23 (0.96–1.57)	0.107
Habitual drinking	1.22 (0.90–1.64)	0.198
Hyperuricemia	1.16 (0.73–1.83)	0.534
Habitual smoking	0.93 (0.67–1.28)	0.641

^AThe base model was adjusted by city and sex. CI, confidence interval; HR, hazard ratio.



ing relationship with increasing radiation dose were dying within 2 years of last visit ($\chi^2=18.93$, $P=0.002$) and smoking habitually ($\chi^2=16.52$, $P=0.006$). Other characteristics that differed among the radiation groups, but with no clear pattern, were prevalent hypertension, hypercholesterolemia, and drinking alcohol habitually. At the last examination, significant differences in hypertension and hypercholesterolemia among the groups disappeared (data not shown). “Death in the 2-year interim” refers to the percentage of participants who died within 2 years since their last visit; the higher this value, the higher the participation rate.

The time since radiation exposure to AF onset was shorter in the Group I than Group V radiation dose group, but there was no significant difference in the age at AF onset among the groups. The Group II and III radiation dose group seemed to have developed AF early because of the high baseline age (data not shown).

Analyses of Continuous Radiation

In the base model accounting for city and sex, neither the linear nor quadratic effects of radiation dose were significant (both $P>0.39$). In the adjusted model, prevalent heart disease, BMI, and prevalent hypercholesterolemia were significant when individually added to the base model (Table 2), and remained significant when all 3 significant

risk factors were included in the adjusted model. In this adjusted model, again, neither the linear nor quadratic coefficients of radiation were significant (both $P>0.33$). We also examined whether each of the risk factors modified the linear or quadratic radiation effects, but none did (all $P>0.54$). The Figure shows the estimated radiation effect on incident AF according to the adjusted model; the HRs of AF at 1 and 2 Gy were 1.00 (95% CI 0.73–1.39) and 0.75 (95% CI 0.45–1.25), respectively.

In the adjusted model and treating the radiation dose as a continuous variable, females had a lower risk of AF than males (HR 0.42; 95% CI 0.33–0.53). The risk of AF in participants exposed in Hiroshima was 0.79-fold (95% CI 0.61–1.02) the risk of participants originally from Nagasaki. HRs for the 3 risk factors differed by no more than 0.06 from individually estimated HRs in Table 2.

Analyses of Categorized Radiation

Table 3 provides AF HRs estimated for the categorized radiation doses in both the base and adjusted models. In both models, AF risk appeared to increase for the lower dose categories, with the highest HR in Group II (radiation dose 0.115–0.272 Gy). AF risk then decreased with increasing dose category, with HRs for Groups IV and V being at or below unity (i.e., with risks lower than that of the control group). Overall, radiation dose categories did not contribute significantly to either model ($\chi^2=7.45$ and $P=0.189$ for the base model; $\chi^2=8.98$ and $P=0.110$ for the adjusted model). We note that although the 95% CI for Group II does not include HR=1, this CI is not adjusted for multiple testing; all the Bonferroni-adjusted CIs (i.e., 99% CIs) contained HR=1.

The HRs of the other cofactors in the adjusted model (city, sex, prevalent heart disease, BMI, and prevalent hypercholesterolemia) differed little from estimates in the adjusted model treating radiation dose as continuous; corresponding estimates were within 6% of each other (data not shown).

Discussion

Although we originally hypothesized that increasing exposure to ionizing radiation would be associated with an increased risk of AF, our findings do not support this hypothesis. An observed possible positive association with AF was limited to those exposed to categorized doses ranging from 0.115 to 0.272 Gy (Group II); otherwise, we found no consistent evidence of a positive association between radiation dose and AF risk. The participants in Group II were older and hypertension was more prevalent in this

Radiation dose category	Secondary base model ^B	Secondary adjusted model ^C
Control	Reference	Reference
Group I	1.14 (0.77–1.69)	1.24 (0.84–1.84)
Group II	1.45 (1.02–2.08)	1.51 (1.05–2.16)
Group III	1.29 (0.89–1.87)	1.38 (0.95–2.01)
Group IV	0.99 (0.66–1.48)	1.03 (0.69–1.54)
Group V	0.81 (0.52–1.28)	0.83 (0.53–1.31)

^ASubjects were divided into six groups according to radiation dose (Control [<0.005 Gy] and 5 equal-sized groups based on radiation dose quintiles; see **Table 1**). ^BThe base model included city, sex, and radiation dose category. ^CThe adjusted model included city, sex, heart disease, body mass index, hypercholesterolemia, and radiation dose category. CI, confidence interval; HR, hazard ratio.

group than in the other dose groups. These results did not change after including age at the time of bombing in the analysis (data not shown). Cologne and Preston reported that life expectancy decreased with increasing radiation dose among atomic bomb survivors, especially among those in the high-dose (>1 Gy) group.³⁴ This is one of the reasons for differences in baseline age among the dose categories. Although we cannot explain the reason why this low dose group has a higher risk of AF, we did find that AF risk tended to decrease with increasing radiation dose (albeit not significantly) in both the adjusted linear-quadratic model and adjusted categorized radiation model.

There may be several potential explanations for the general lack of a positive association between radiation dose and AF risk. The present study was adequately powered to detect HRs between 1.15 for higher baseline AF rates and 1.40 for lower AF rates. Among the subjects overall, the AF rate was 1.5 per 1,000 person-years. Therefore, it is possible that the null findings may be due to a true lack of causal relationship between radiation and AF. Although it has been reported that high-dose radiation up to 60 Gy due to radiotherapy affects the cardiac conduction system^{16,17} and AF,¹⁸ a previous study of ECG abnormalities among atomic bomb survivors indicated no association with radiation dose.²¹ The present study is the first study to investigate AF incidence among atomic bomb survivors (exposed to 0–4 Gy) over 4 decades with a high participation rate ($>70\%$), and the results supports those from our previous studies.^{19–21}

The pathophysiology of AF is complex, including inflammation, oxidative stress, fibrosis, autonomic changes, and a substantial genetic component.⁷ The causes of AF are varied and can occur concurrently. In the present study, an AF subtype analysis based on the underlying causes was not conducted because we were unable to separate genetic AF from other causes. The heterogeneous and multifactorial features of AF may have made the detection of a potential association with radiation difficult.

The incidence rate of AF in the present study was 1.56 per 1,000 person-years, and this rate appears to be lower than that reported in US^{3,35} and European¹ studies, as well as elsewhere in Japan.^{31–33} However, after taking into consideration the facts that the baseline period of the present study was earlier (1967–1969), age at baseline was younger (22–90 years), and females predominated (65.8%), the incidence rate in this study is concordant with that in other reports.

Of the cardiovascular disease risk factors (sex, hypertension, hypercholesterolemia, hyperuricemia, heart disease, BMI, and smoking and drinking habits) included in the

present study as cofactors when examining the relationship between radiation dose and AF incidence, male sex, heart disease, and BMI were positively associated with AF incidence. These positive associations with AF incidence corroborate results reported by others.^{36,37} In the present study, those with hypercholesterolemia were less likely to develop AF; others have found similar results, although not always statistically significant,^{33,35–37} and radiation exposure has been found to be positively associated with cholesterol levels³⁸ and negatively associated with BMI.³⁹ Therefore, it is unlikely that the null or non-significant negative associations of radiation dose with incident AF are due to changes in total cholesterol and BMI among atomic bomb survivors, whereby exposure to higher doses of radiation leads to higher cholesterol and lower BMI, both of which reduce the likelihood of developing AF. For the remaining risk factors (hypertension, hyperuricemia, smoking, and alcohol drinking), associations with AF incidence were weak to negligible in our cohort. Regarding hypertension, some have found AF risk is reduced in those on antihypertensive treatment using angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.^{40,41} Proportionately more atomic bomb survivors may take these medications than those not exposed to radiation because atomic bomb survivors tend to have higher blood pressure.²³ The finding of increased risk due to radiation exposure may be diminished by these treatments. Several studies found increased AF risks for those with hyperuricemia;^{9,42} a similar effect was found in the present study, although it was not significant. Smoking habits have been reported to be associated with increased AF risk.³³ However, our cohort self-reported both current and past habitual smoking via mail survey or interview at examination, thus possibly explaining the negligible (negative) association. Drinking alcohol, especially heavy drinking, has been found to be associated with increased AF risk.³² In the present study, AF risk was also increased with reported alcohol drinking, but the CI was wide, likely due to a lack of data on the amount of alcohol typically consumed. In addition, our cohort was largely female, which, in Japan, may lead to an assumption of relatively fewer heavy drinkers than in a cohort with a higher proportion of males.

Study Limitations

Some limitations should be mentioned. First, the identification and classification of AF is a potential limitation of the present study. The type of AF (paroxysmal, persistent, or chronic) could not be definitively classified in the present epidemiological study. Patients with paroxysmal AF that did not progress to chronic state or were asymptom-

atic could have been missed even through once every 2 years follow-up. This could have led to an underestimation of the number of cases of AF. Second, confounding due to unmeasured or unincorporated factors may have affected the present results. In particular, because plasma glucose was not measured among all participants at baseline, diabetes was not included as a cofactor. Third, a bias due to death would arise if participants with incident AF did not attend their next examination because of death and a proportion of those deaths were due to AF that developed. However, we did not check the cause of death in the present study. Further studies considering these problems may address these limitations.

Strengths

This study has important strengths, including its prospective design, a large sample size, long-term, once every 2 years follow-up, a high participation rate, reliable exposure information, and meticulous ascertainment of AF cases. The prospective design of the study reduced the likelihood of selection bias and recall bias. Close follow-up and biennial ECGs reduced the potential for missing AF events, including asymptomatic cases, especially if chronic.

Conclusions

We found no clear evidence of positive associations between atomic bomb radiation exposure (<4 Gy) and the incidence of AF.

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Disclosures

K.M. is a member of *Circulation Reports*' Editorial Team. The remaining authors have no conflicts of interest to declare.

IRB Information

The Human Investigation Committees of the RERF approved the study protocol (RP A1-15).

Data Availability

The data will be made available by request to the RERF after ethical and scientific institutional review. Those interested can contact the corresponding author.

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