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High Initial-dose Dependency of Cerebrovascular Disease Mortality among Female Survivors of the Hiroshima Atomic Bomb Exposed in Teens: A Cohort Study, 1970-2010

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ABSTRACT

Several studies have been conducted on cerebrovascular disease mortality in Atomic bomb survivors. Previous studies have investigated the relationship between mortality and initial radiation dose after adjusting for the effects of sex and age at the time of the bombing (ATB), and detected a weak (but statistically significant) dose-response relationship was detected. The objective of the present study was to examine whether the sex- and age ATB-specific cerebrovascular disease mortality among Hiroshima atomic bomb survivors can be explained by the initial radiation dose. At Hiroshima University, a cohort study has been conducted with Hiroshima Atomic Bomb Survivors (ABS) since 1970. We selected 30,378 subjects from the ABS who were exposed at 3.5 km or less from the hypocenter and still alive on January 1, 1970. These subjects were followed up until December 31, 2010. The cohort data were stratified with respect to sex and age ATB into 10-year age groups. For each stratum, using Cox regression, we performed survival analyses of the risk of cerebrovascular mortality using the initial radiation dose and the exposure distance (the ground distance between the exposure location and the hypocenter) as explanatory variables. The results indicated that the risks to females exposed at 10 to 19 years old were highly dependent on the initial radiation dose (hazard ratio: 1.51, $p < 0.001$), while the risks to males were not. There might exist some radiation exposure effects limited to women who were in their teens at the time of exposure. However, the background mechanisms remain unclear, necessitating further study.

Key words: *Atomic bomb survivors, Cerebrovascular disease, Dose-response relationship, Exposure-distance*

Arteriosclerotic cardiovascular disease is now the cause of death of approximately one in three Japanese people. In the 1960s, cerebrovascular disease was the leading cause of death in Japan, but it is now the third leading cause, with a dramatically decreasing tendency since the 1970s[7]. With approximately 70 years having passed since the atomic bombs were dropped, almost all atomic bomb survivors (*hibakusha*) now belong to the generation in which the onset of cardiovascular disease is common, and the effects of radiation on cardiovascular disease have been well studied. However, we have not yet clearly grasped the impact of exposure to radiation from atomic bombs on cerebrovascular disease. Preston et al observed a significant correlation with initial radiation dose after adjusting for the effects of sex and age at the time of the bombing (ATB), reporting an excess relative risk of death due to cerebrovascular disease of 0.12 (90% confidence interval: 0.02–0.22) per Sv of radiation dose[22]. Shimizu et al also observed a non-significant ($p = 0.23$) correlation with radiation dose, reporting an excess relative risk per Gy of 36%, 9%, 15% and 5% for ages < 10, 10-19, 20-39, and ≥ 40[25]. These studies examined the relationship between the initial radiation dose (initial dose) and the mortality risk. Atomic bomb radiation exposure can be divided into two types: direct exposure (gamma-ray as well as immediate and delayed neutron radiations) from the initial explosion and indirect exposure from residual radiation comprising neutron activated radiation in

soil and other materials as well as fallout from the nuclear explosion. The initial dose is determined by the ground distance from the hypocenter to the victim's location at the time of exposure (exposure distance) and shielding conditions assessed from information provided by exposed persons, such as being in buildings or other structures at the time of the bombing. If all of this information is available, the individual direct, initial radiation dose may be estimated. However, it is almost impossible to estimate the individual amount of exposure from residual radiation, because of uncertain or lacking information on individual movements and activities just after the bombing.

The impact of residual radiation as a health hazard has traditionally been assumed to be negligible[12,26]. However, it is becoming clear that the increase in several health risks related to *hibakusha* cannot be explained by the effect of initial dose alone[24]. Tonda et al[28] showed that the geographical distribution of the risk of solid cancer mortality among Hiroshima *hibakusha* is not circular asymmetry around the hypocenter. Recently, Kerr et al[13] reported that the health risk among atomic bomb survivors in Hiroshima and Nagasaki of residual radiation from neutron-activated radionuclides in the airburst's dust stem and pedestal and in uplifted soil might be not negligible. Tonda et al[27] suggested the impact of indirect exposure as a factor in the increased leukemia risk for those who entered Hiroshima City on 6 August 1945. Otani et al[17] reported that the mortality risk for malignant neoplasms (excluding leukemia) was significantly higher for those who entered Hiroshima City on 6 August 1945. The results of both of those studies apply as well to *hibakusha* who were directly exposed age ATB since they were also exposed to residual radiation. Ohtaki et al[16] reported that the mortality rate for solid cancers among *hibakusha* is influenced not only by the initial dose of radiation but also by indirect exposure.

In observational epidemiologic studies, confounding is one of the major limitations. Shimizu et al[25] indicated that smoking, alcohol intake, education, occupation, obesity, and diabetes had had almost no impact on radiation risk estimates for stroke. In our study, it was impossible to analyze the data by adjusting confounding factors such as high blood pressure, a smoking habit, etc. For even if the association between radiation risk and cerebrovascular disease is actually due to some confounding factor so that radiation risk is not causally related to cerebrovascular disease, screening for radiation risk can nevertheless be useful because it permits us to identify people who are at high risk for the disease. The objective of the present study was to examine whether the sex- and age ATB-specific cerebrovascular disease mortality among *hibakusha* can be explained solely by the initial radiation dose.

SUBJECTS AND METHODS

For the present study we used the database of Atomic Bomb Survivors (ABS) that has been managed by the Research Institute for Radiation Biology and Medicine (RIRBM) of Hiroshima University[14]. The ABS differs from the Life Span Study (LSS) of the Radiation Effects Research Foundation (RERF), which that is based on subjects throughout Japan, in that the subjects in the ABS are restricted to Atomic bomb survivors residing in Hiroshima Prefecture. From the ABS, we chose for analysis 30,378 subjects (11,683 males and 18,695 females) who satisfied the following conditions: (i) alive and recognized as an atomic bomb survivor as of January 1, 1970 (the start of the observation period) and (ii) information available on the coordinates of their location at the time of atomic bomb exposure (abbreviated as "location at exposure"). The distance from the hypocenter to the location at exposure (abbreviated as "exposure distance") was within 3.5 km. These subjects were followed until December 31, 2010 for death from cerebrovascular disease (number of deaths: 1,006 among males, 1,945 among females). The death information including the cause of death was obtained from the Vital Statistics Death Schedules which are based

Table 1.1. Number of subjects, events, and censored cases by sex and age at time of exposure (ATB)

(Males)

age ATB (yrs)	number of subjects	number of events	number of censored cases†	number of surviving cases††
[0, 10)	3472	46	555	2871
[10, 20)	2877	121	1179	1577
[20, 30)	1139	105	812	222
[30, 40)	1684	253	1321	110
[40, 50)	1725	318	1322	85
[50, 60)	703	146	526	31
[60, 70)	78	16	61	1
[70, 80)	5	1	4	0
total	11683	1006	5780	4897

(Females)

age ATB (yrs)	number of subjects	number of events	number of censored cases†	number of surviving cases††
[0, 10)	3332	23	1129	2180
[10, 20)	3701	104	1291	2306
[20, 30)	3708	279	2077	1352
[30, 40)	3701	557	2954	190
[40, 50)	2943	638	2301	4
[50, 60)	1112	294	818	0
[60, 70)	188	49	139	0
[70, 80)	10	1	9	0
total	18695	1945	10718	6032

†Number of persons who emigrated out of Hiroshima prefecture or who died from other causes of death.

††Number of persons still alive at 31 Dec 2010.

Table 1.2. Number of subjects, events, and censored cases by sex and exposure distance

(Males)

distance (km)	number of subjects	number of events (CVD)	number of censored cases†	number of surviving cases††
[0.0, 0.8)	1	0	1	0
[0.8, 1.0)	159	14	103	42
[1.0, 1.2)	454	52	257	145
[1.2, 1.4)	967	100	498	369
[1.4, 1.6)	1223	90	610	523
[1.6, 1.8)	994	94	506	394
[1.8, 2.0)	705	66	373	266
[2.0, 2.5)	1083	97	549	437
[2.5, 3.0)	3959	310	1895	1754
[3.0, 3.5)	2138	183	988	967
total	11683	1006	5780	4897

(Females)

distance (km)	number of subjects	number of events (CVD)	number of censored cases†	number of surviving cases††
[0.0, 0.8)	5	0	2	3
[0.8, 1.0)	275	27	200	48
[1.0, 1.2)	909	100	582	227
[1.2, 1.4)	1806	210	1089	507
[1.4, 1.6)	2380	271	1425	684
[1.6, 1.8)	1768	182	1048	538
[1.8, 2.0)	1156	128	650	378
[2.0, 2.5)	1354	136	759	459
[2.5, 3.0)	5526	543	2987	1996
[3.0, 3.5)	3516	348	1976	1192
total	18695	1945	10718	6032

†Number of persons who emigrated out of Hiroshima prefecture or who died from other causes of death.

††Number of persons still alive at 31 Dec 2010.

Table 1.3. Number of subjects, events, and censored cases by sex and dose categories

(Males)

dose(Sv)	number of subjects	number of events (CVD)	number of censored cases†	number of surviving cases††
[0.00, 0.01)	6931	561	3305	3065
[0.01, 0.05)	682	75	385	222
[0.05, 0.1)	731	65	358	308
[0.1, 0.2)	972	84	503	385
[0.2, 0.4)	1027	84	532	411
[0.4, 0.6)	399	37	186	176
[0.6, 0.8)	250	27	116	107
[0.8, 1.0)	190	28	112	50
[1.0, 1.5)	193	16	102	75
[1.5, 2.0)	111	10	62	39
[2.0, 6.0)	197	19	119	59
total	11683	1006	5780	4897

(Females)

dose(Sv)	number of subjects	number of events (CVD)	number of censored cases†	number of surviving cases††
[0.00, 0.01)	9960	975	5466	3519
[0.01, 0.05)	1170	134	684	352
[0.05, 0.1)	1339	139	783	417
[0.1, 0.2)	1833	212	1094	527
[0.2, 0.4)	1941	227	1174	540
[0.4, 0.6)	771	85	444	242
[0.6, 0.8)	448	44	266	138
[0.8, 1.0)	397	48	264	85
[1.0, 1.5)	341	31	216	94
[1.5, 2.0)	173	20	101	52
[2.0, 6.0)	322	30	226	66
total	18695	1945	10718	6032

†Number of persons who emigrated out of Hiroshima prefecture or who died from other causes of death.

††Number of persons still alive at 31 Dec 2010.

on the official death certificates. Subjects who were alive at the end of follow-up, migrated outside Hiroshima Prefecture, or died from other causes were treated as censored (5,780 males and 10,718 females). Numbers of subjects categorized by age ATB and exposure distance are shown in Table 1.1 and 1.2 for each sex, respectively. From these tables, it is indicated that about 40% of the subjects were under 20 years-old at the bombing in this cohort data, and that approximately 5% of the subjects were bombed near the hypocenter with the distance less than 1.2 km.

1. Radiation dosimetry

To access the effect of initial radiation dose on the human body (unit of measurement: Sv), we used the red bone marrow absorbed neutron and gamma doses (unit of measurement: Gy) estimated using the Atomic Bomb Survivor 1993 Dose (which is referred to as ABS93D)[8]. The radiation dose calculated with ABS93D is based on the initial radiation exposure only, as is DS86, and ignores the effects of residual radiation[20-22]. The extent of overlap between survivors in the ABS and the LSS was examined by Hayakawa et al[6] in which

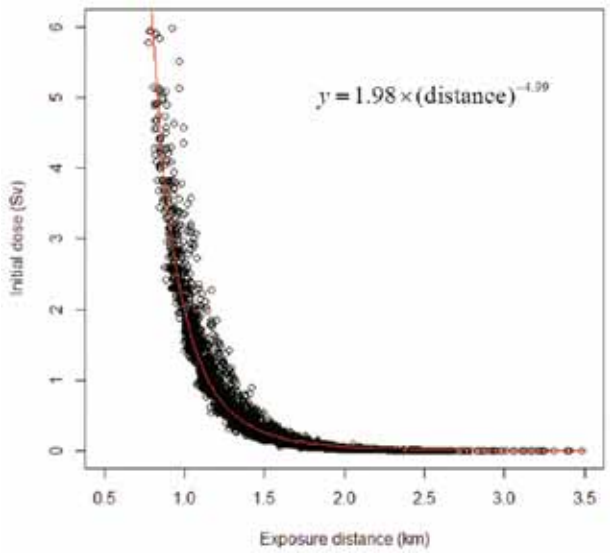

Fig. 1. Scatterplot of initial radiation dose versus exposure distance

it was shown that the dose estimates of the ABS were close to those of the LSS among overlapping subjects. However, it has not yet been investigated

how ABS93D corresponds with DS02. Table 1.3 shows the sex-specific numbers of subjects categorized by initial dose. About 70% of the subjects belong to the low-doses (less than 100 mSv) exposure group and approximately 4% belong to the high-doses (1.0 Sv or more) exposure group. Figure 1 shows a scatterplot of subjects' initial radiation dose versus exposure distance with the fitted curves based on a power function of exposure distance. It is noted that the initial radiation dose for the subjects can be roughly fitted by an inverse of 5th power function of exposure-distance.

2. Kaplan-Meier Curves

Assuming that there would be sex differences in the risk of cardiovascular disease[10] and a dependency on age ATB among *hibakusha*, we stratified the cohort data by sex and age ATB, and calculated the probability of not dying from cerebrovascular diseases (abbreviated simply as "survival probability") by initial dose and exposure distance using the Kaplan-Meier method[11]. Figures 2.1~2.4 show the survival rate for each sex- and age ATB-specific stratum. For these strata, we compared the survival curves of the cohorts exposed to low doses (less than 100 mSv) and high doses (1.0 Sv or more), and the survival curves of the cohorts exposed at short distances (less than 1.2 km) and long distances (2.0 km or more) using the log-rank test.

3. Cox Regression analysis

To quantify the effect of initial dose and exposure distance in detail, we conducted a survival analysis using a mathematical model as defined below. Based on the epidemiological observation that the mortality risk from cerebrovascular disease rises exponentially with increasing age[30], the hazard at attained age t, which incorporates the effect of the initial radiation dose D at age a (the initial-dose model), is expressed by:

$$h(t \mid D, a) = \exp\left(\beta_a D\right) \cdot \exp\left\{g(t, t-a+1945) + \delta\right\},$$

where β_a is the regression coefficient for the impact of the initial dose among *hibakusha* who were age a at the time of exposure, while g (t,y) is a logarithmic function of calendar year (y) and age (t) for the cerebrovascular disease mortality rate in all of Japan during the period 1970 to 2010, which is specified approximately by a quintic polynomial equation of t and y. The parameter δ denotes a coefficient expressing the logarithmic value of the background relative mortality risk of cerebrovascular disease for the Hiroshima *hibakusha* compared with the whole of Japan. Further, to investigate the impact of exposure distance, the following function of exposure distance r (in km, where the value for r = 2 km or more was assumed to be 0) was used as an alternative variable in place of initial radiation dose D,

$$D^*(r \mid \mu) = \begin{cases} \dfrac{\mu - r}{\mu - 1}, & r < \mu, \\ 0 \quad , & r \geq \mu. \end{cases} \qquad (1 < \mu \leq 2)$$

where μ is a parameter denoting the threshold of exposure-distance effect. Thus the distance-function model is expressed by:

$$h(t \mid D^*, a) = \exp\left(\beta_a D^*\right) \cdot \exp\left\{g(t, t-a+1945) + \delta\right\}$$

The cohort data were classified by sex and by age ATB into eight strata—[0, 10), [10, 20), [20, 30), and [30, 80) groups for each sex—and a time-dependent Cox regression analysis[2,3] was applied to each stratum with a hazard model using initial dose D or exposure-distance function D^*, where the estimated regression coefficient β_a expresses the stratum-averaged effect of initial radiation dose or exposure distance and the estimated parameter μ is a location parameter in the-exposure-distance function. To fit the model, we adopted the optimize function[23] in the R software (version 3.0.0). Since it is noted that the model with the minimum AIC has the best goodness of prediction, we used AIC to select the optimal model from the three models (the initial-dose model, the distance-function model and the null model with neither initial dose nor distance function as explanatory variables).

The null model is expressed by:

$$h(t \mid a) = \exp\left\{g(t, t-a+1945) + \delta\right\}$$

Significance tests in all cases were at the 5% level with a two-tailed test.

RESULTS

Kaplan-Meier survival curves by initial dose for men and women are shown in Figs. 2.1 and 2.2, respectively, and those by exposure distance are shown in Figs. 2.3 and 2.4. For men, the log-rank test indicated no significant difference between the low-dose (less than 100 mSv) and high-dose (1.0 Sv or more) exposure groups in any age-ATB stratum (Fig. 2.1). Similarly, no significant differences were observed in survival rates between the short-distance (less than 1.2 km) and long-distance (2.0 km or more) groups in any age-ATB stratum (Fig. 2.3). For women whose age ATB was between 10 and 19, the survival rate of the high-dose (1.0 Sv or more) group was significantly lower than that of the low-dose (less than 100 mSv) group (Fig. 2.2). Further, for women whose age ATB was either between 10 and 19 or 50 or more, the survival rate in the short-distance (less than 1.2 km) group was significantly lower than that in the long-distance (2.0 km or more) group (Fig. 2.4). In all other strata of age ATB, no significant differences in survival rates were observed.

Tables 2.1 and 2.2 display estimated values and significance of the regression coefficient β. In all

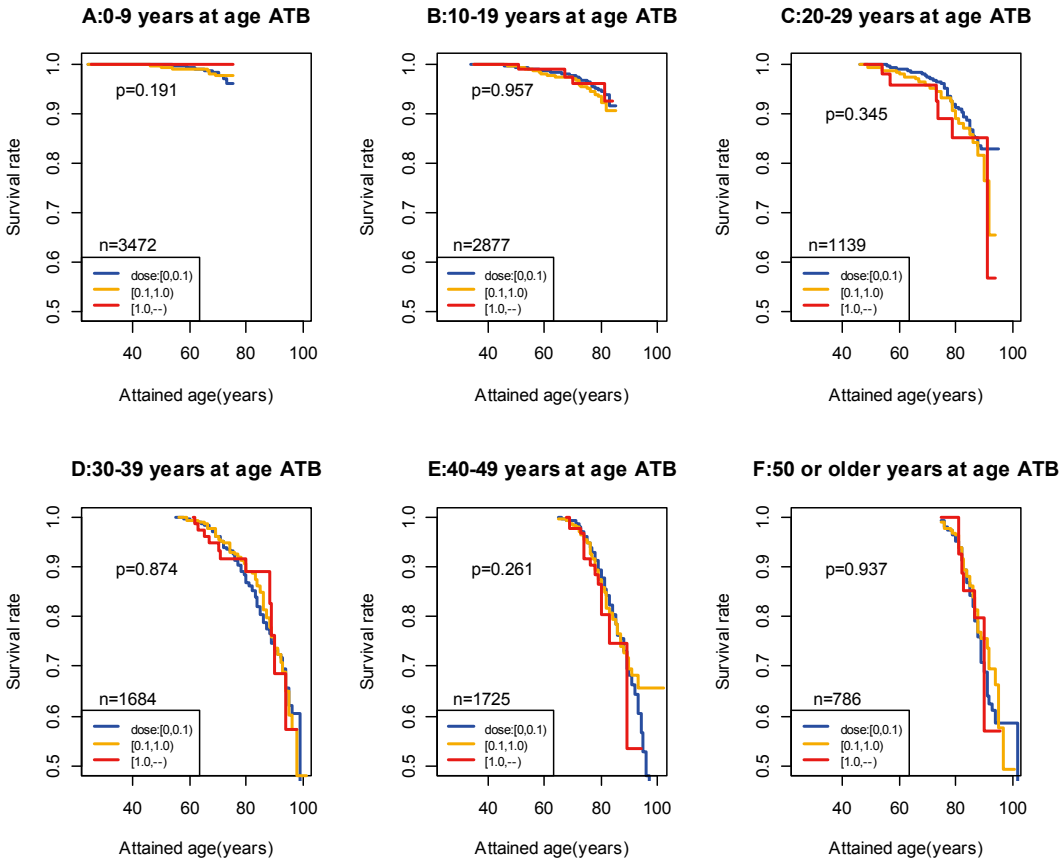

Fig. 2.1. Kaplan-Meier survival curves by initial radiation dose for males stratified by age ATB in 10-year age group. The p-value indicates the statistical significance of the difference between the low-dose group (< 0.1 Sv) and the high-dose group (>1.0 Sv).

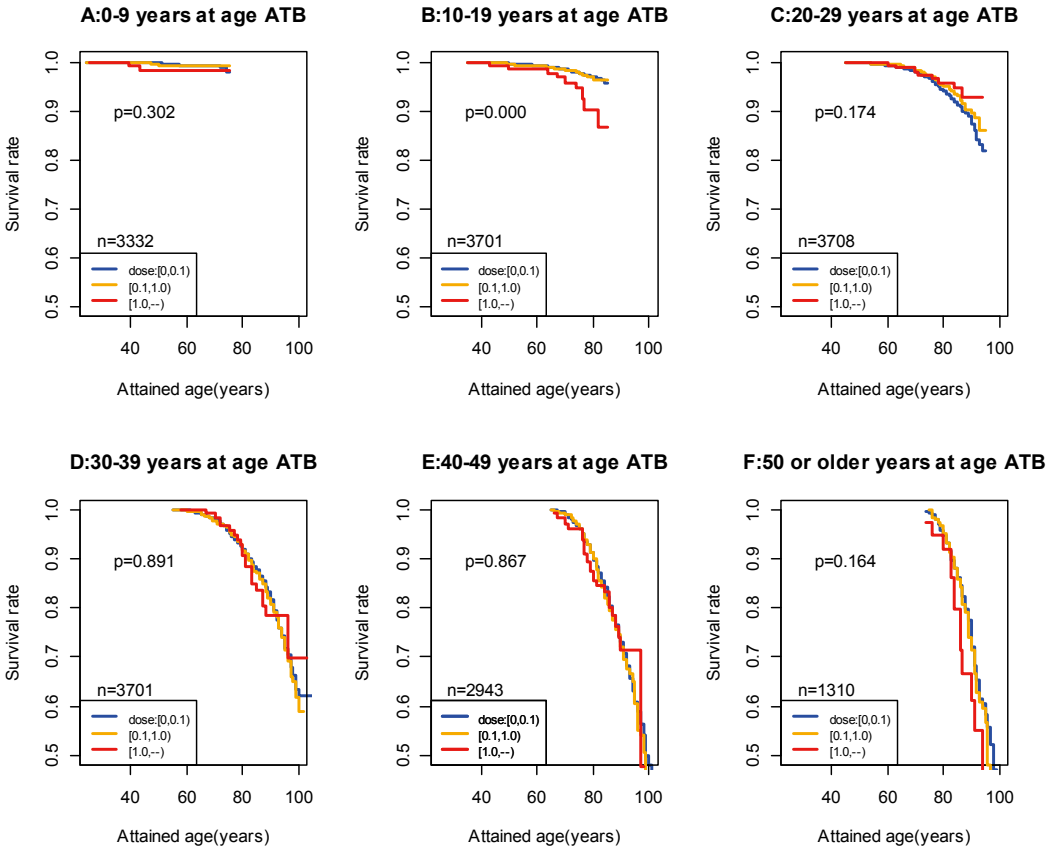

Fig. 2.2. Kaplan-Meier survival curves by initial radiation dose for females stratified by age ATB in 10-year age group. The p-value indicates the statistical significance of the difference between the low-dose group (< 0.1 Sv) and the high-dose group (>1.0 Sv).

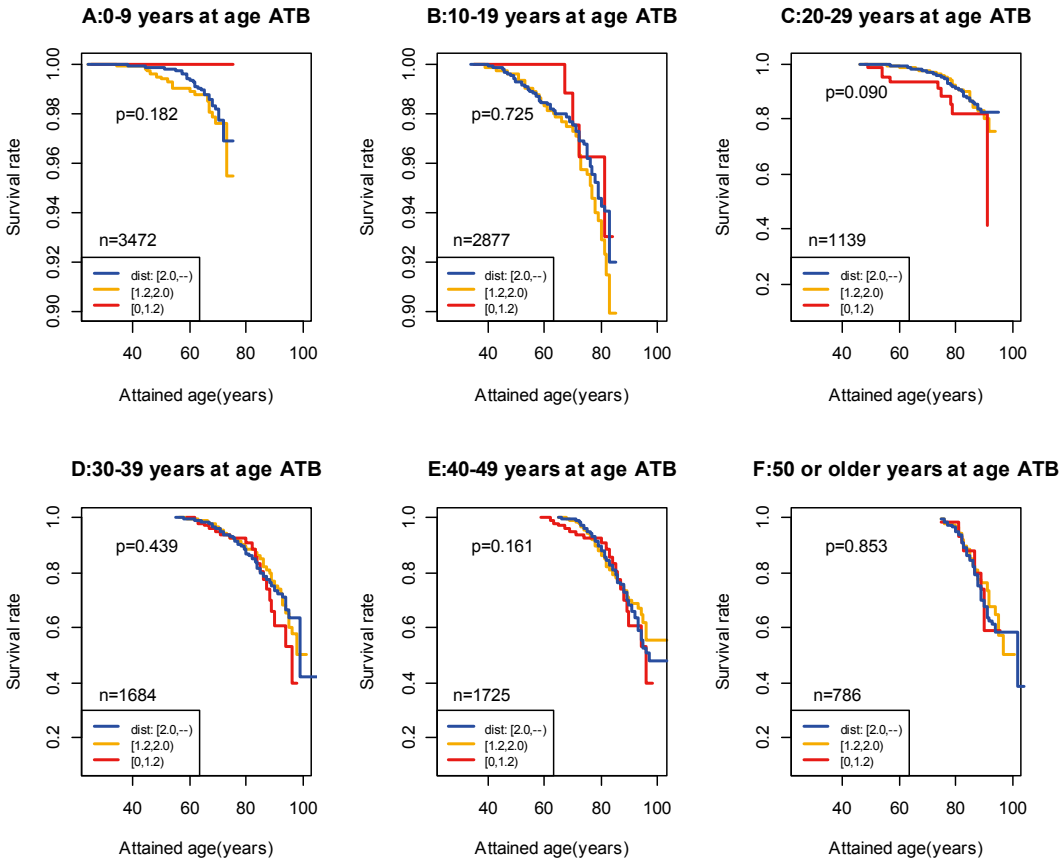

Fig. 2.3. Kaplan-Meier survival curves by exposure-distance for males stratified by age ATB in 10-year age group. The p-value indicates the statistical significance of the difference between the short-distance group (<1.2 km) and the long-distance group (>2.0 km).

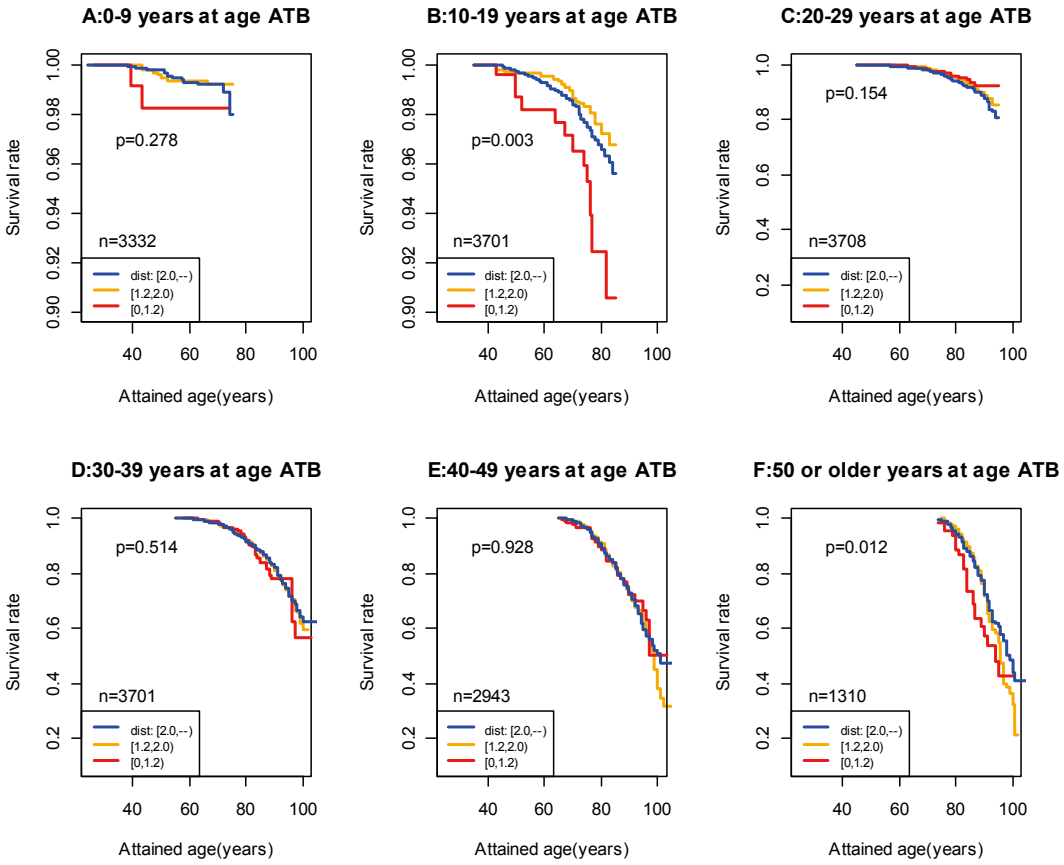

Fig. 2.4. Kaplan-Meier survival curves by exposure-distance for females stratified by age ATB in 10-year age group. The p-value indicates the statistical significance of the difference between the short-distance group (<1.2 km) and long-distance group (>2.0 km).

Table 2.1. Sex- and age ATB-specific estimated coefficients (β) of the dose effect

(Males)

age ATB	coef.	s.e.	95%lower	95%upper	p-value
[0, 10)	-0.513	0.558	-1.606	0.579	0.36
[10, 20)	0.033	0.212	-0.382	0.449	0.87
[20, 30)	0.224	0.173	-0.114	0.562	0.19
[30, 80)	0.107	0.743	-0.038	0.252	0.15

(Females)

age ATB	coef.	s.e.	95%lower	95%upper	p-value
[0, 10)	0.330	0.324	-0.305	0.964	0.31
[10, 20)	0.410**	0.115	0.185	0.636	<0.001
[20, 30)	-0.115	0.142	-0.394	0.163	0.42
[30, 80)	0.031	0.058	-0.083	0.145	0.60

**: $p < 0.01$

Table 2.2. Sex- and age ATB-specific estimated coefficients (β) of the distance effect

(Males)

age ATB	coef.	s.e.	95%lower	95%upper	p-value
[0, 10)	-29.343	63.225	-153.262	94.577	0.64
[10, 20)	0.275	0.322	-0.357	0.906	0.39
[20, 30)	0.437	0.361	-0.270	1.144	0.23
[30, 80)	0.263	0.158	-0.047	0.572	0.10

(Females)

age ATB	coef.	s.e.	95%lower	95%upper	p-value
[0, 10)	1.139	0.708	-0.248	2.526	0.11
[10, 20)	1.071**	0.279	0.524	1.617	< 0.001
[20, 30)	-0.320	0.209	-0.730	0.089	0.12
[30, 80)	0.086	0.098	-0.106	0.278	0.38

**: $p < 0.01$

models for men, no significant contribution was detected for either initial dose or exposure distance. In women, a significantly high contribution was detected for the influence of initial dose (hazard ratio: 1.51, $p < 0.001$) only if their age ATB was between 10 and 19.

Table 3 shows estimated values of the parameter μ of the distance function model. Table 4 shows AIC[1)] for the initial dose model, the exposure-distance model, and the null model, applied to each stratum of age ATB. In men whose age ATB was under 10, the distance-function model had the minimum AIC. In women whose age ATB was between 10 and 19, the initial-dose model had the minimum AIC. The null model had the minimum AIC in other age-ATB strata.

DISCUSSION

The principal risk factors for cerebrovascular disease include aging and arteriosclerosis[15)]. The female sex hormone estrogen works to inhibit arteriosclerosis by suppressing increases in LDL cholesterol and raising HDL cholesterol level[19,29)]. Accordingly, during the period of life with plentiful secretion of female sex hormone, women have a significantly lower risk of cardiovascular disease than men[10)]. Thus, sex is a confounding factor influencing risk of mortality from cerebrovascular disease. It is also assumed that many *hibakusha* inhaled fine radioactive particulate material after the explosion, even if they were inside large buildings or in a basement at the time of the explosion, and that behavioral patterns just after the bombing were largely dependent on sex and age ATB, which leads to the deduction that "dose" due to residual radiation must depend on sex and age ATB. Due to the reasons described above, we stratified the *hibakusha's* cohort data according to sex and age ATB, and analyzed the effect of exposure to radiation, separately. Residual radiation comprises neutron activated radiation in soil and other materials as well as fallout from the nuclear explosion. Radioactive contaminants were generated in the neighborhood of the hypocenter and were dispersed with the bomb blast. Because the dose from residual radiation exposure should not be greatly influenced by the degree of shelter from direct radiation at the time of the explosion, the present study also utilized an analysis based on distance from the hypocenter as an alternate index of exposure. The exposure-distance model is thought to be a good alternative to the initial-dose model, in which effects of shielding from direct Atomic bomb radiation were not taken into account. In the exposure-distance model, we assumed that the effect of an exposure-distance of 2.0 km or more was 0.

In our Cox regression analyses, since the follow-up period for this study covers 41 years from 1970

Table 3. Sex- and age ATB-specific estimated parameter (μ) of the exposure-distance function

age ATB	Males	Females
[0, 10)	1.24	1.19
[10, 20)	2.00	1.23
[20, 30)	1.67	2.00
[30, 80)	1.43	1.68

Table 4. AIC of candidate models and differences in AIC between initial-dose and other models

(Males)

age ATB	dose[(a)]	dist[(b)]	null[(c)]	Δdist†	Δnull††
[0, 10)	680.3	678.9	679.5	-1.4	-0.8
[10, 20)	1755.5	1756.8	1753.5	1.3	-2.0
[20, 30)	1315.8	1317.9	1315.2	2.1	-0.6
[30, 80)	9921.6	9922.9	9921.6	1.3	-0.1

(Females)

age ATB	dose[(a)]	dist[(b)]	null[(c)]	Δdist†	Δnull††
[0, 10)	354.2	355.3	353.0	1.1	-1.2
[10, 20)	1624.8	1625.1	1631.2	0.3	6.4
[20, 30)	4222.9	4223.2	4221.6	0.3	-1.3
[30, 80)	23467.2	23468.7	23465.4	1.5	-1.8

†***(b)*–*(a)***: The difference in AIC between the initial-dose model and distance-function model

††***(c)*–*(a)***: The difference in AIC between initial-dose model and null model

※ Initial radiation dose model has one, distance-function model has two, null model has no unknown parameters.

and the age-adjusted mortality rate of cerebrovascular disease among the general population in Japan decreased dramatically during this period[7], we took these changes of background risk into account in our analysis by allowing for effects of calendar year. Kaplan-Meier curves with log-rank tests and Cox regression analyses results both suggested that, aside from women whose ages were 10 to 19 ATB, the effect of neither initial dose nor exposure distance was statistically significant, which suggests that radiation exposure has no direct impact on mortality due to cerebrovascular disease. In contrast, significant effects of both initial dose and exposure distance were detected among women whose age ATB was between 10 and 19. It is unlikely that radiation exposure had an effect only in this group. The physical and mental damage suffered as a result of the bombings, such as loss of family members and the subsequent deterioration of lifestyle and environment, cannot be ignored. Cerebrovascular diseases are considered to be a type of lifestyle disease, and their onset and progression is influenced by lifestyle factors such as exercise habits, smoking, and drinking[5,15]. For women whose age ATB was in the teens, the estimated effects of initial dose and exposure distance were significant. However, the numbers of female subjects were 2, 55 and 193 for exposure distance < 0.8 km, 0.8 - 1.0 km and 1.0 - 1.2 km. Therefore, it might be accidental that the estimated effect of exposure distance was significant because of the small sample size. There might also exist some effect of radiation exposure limited to women in their teens at the time of exposure; however, the background mechanisms remain unclear, necessitating further study.

Deaths from other diseases were treated as censored in the present study. Strictly speaking, it would be appropriate for these to be treated as competing risks[9]. We may disregard the effects of exposure due to the atomic bomb such as death from explosion including acute radiation symptoms and those due to malignant tumors, etc., which might reduce the observed excess mortality from cerebrovascular disease through the competing risk effect. Ozasa et al[18] reported that the sex-averaged excess relative risk per Gy was 0.42 for all solid cancer at age 70 years-old after exposure at age 30 and that female susceptibility was about twice as high as the male one. In particular, heart disease, which shares many of the same risk factors[4], resulted in many deaths where cerebrovascular disease went undetected. Owing to a competing risk with other causes of death, such as that from heart disease, cerebrovascular disease mortality must be underestimated. In this paper, we showed that the impact was understimated for the young or middle-aged because of their low mortality. The same applies for death in the elderly due to solid cancers. In addition, as the present study was commenced in 1970, 25 years after exposure to the Atomic bomb, it is likely that many deaths occurred prior to the start of the cohort study not only from the effects of the explosion but also due to acute radiation syndrome. Therefore, people with a relatively high risk of death from radiation-related cerebrovascular disease might have been selectively excluded. As a result, we may have underestimated the excess risk for the effect of exposure to the atomic bomb.

Our study had the same limitation as LSS by Ozasa et al[18] in RERF due to analyses without adjusting for the possible effects of confounding factors, since such information was not available in the large cohort studies. For even if some confounding factors mislead the effect of radiation risk to cerebrovascular disease mortality, the result of this study must be a clue toward clarifying how radiation risk affects cerebrovascular disease.

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