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High Excess Risk of Heart Disease Mortality among Hiroshima Atomic Bomb Male Survivors Exposed Near the Hypocenter

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ABSTRACT

Heart disease (HD) mortality is the second leading cause of death in Japan. The HD mortality risk among Atomic bomb survivors is slightly positive but shows a statistically significant dose-response relationship with initial radiation dose, as reported by the Radiation Effects Research Foundation. In that report, dosimetry was based on initial radiation only, with the effect of indirect radiation dose not taken into consideration. The atomic bomb radiation, however, consisted of both initial and residual radiation. We reevaluated the dose-response relationship for HD mortality using exposure distance (ground distance between the location where exposed and the hypocenter) as a surrogate indicator of radiation dose. At Hiroshima University, a cohort study has been conducted with Hiroshima Atomic Bomb Survivors (ABS) since 1970. We selected 29605 subjects from the ABS who were exposed at 3.5 km or less from the hypocenter and alive on January 1, 1970. These subjects, referred to as "Hiroshima *hibakusha*" in this paper, were followed until December 31, 2010. We stratified the cohort data with respect to sex and age at the time of bombing (ATB) into 10-year age groups. For each stratum, by applying an extended Cox regression model with time-dependent covariates, we analyzed the risk of HD mortality using either initial radiation dose or exposure distance as an explanatory variable. The results indicate a high excess risk in males and older age ATB females who were exposed near the hypocenter. This difference may be explained by the effect of female sex hormone on the circulatory system among young age ATB females. Some unknown risk factor related to exposure distance was also implicated in the elevated risk of HD among the Hiroshima *hibakusha*, especially in males. This necessitates further study.

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

Heart disease (HD) was ranked the second leading cause of death in Japan after cancer as of 2010[13]. Among cohort studies of the mortality risk of HD in the general population, the Framingham Heart Study and the Hisayama Study are well known. Sytkowski et al showed that morbidity and mortality among females were comparatively low during the follow-up in Framingham residents from 1950 to 1989[26]. Ueda showed that the rate of development of symptoms of ischemic heart disease rose with increasing age, with rates in males higher than in females in a follow-up study of Hisayama residents from 1961 to 1984[29].

HD mortality risks among atomic bomb survivors have been described in several reports published by the Radiation Effects Research Foundation[19,24]. In those studies, dosimetry was based on initial radiation only[7,14], with the effect of indirect radiation not taken into consideration. In fact, it is known that atomic bomb radiation exposure comprises two types: direct exposure (gamma-ray as well as prompt 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. Lauk et al reported serious heart disease induced by X-ray doses of 10 Gy or more in rats[11]. However, it is becoming clear that the increase in several health risks in *hibakusha* cannot be explained by the effect of initial dose alone[23]. Recently, Kerr et al reported that the health risk among atomic bomb survivors in Hiroshima and Nagasaki for residual radiation from neutron-activated radionuclides in the airburst's dust stem and pedestal and in surface soil might not be negligible[9]. Tonda et al showed that the geographical distribution of solid cancer mortality risk among Hiroshima *hibakusha* is not circular but asymmetric around the hypocenter[28]. Tonda et al suggested the impact of indirect exposure as a factor in the increased leukemia risk for those who entered Hiroshima City on 6 August 1945[27]. Otani et al reported that the risk of mortality from malignant neoplasms (excluding leukemia) was significantly higher for those who entered Hiroshima City on 6 August 1945[18]. Ohtaki et al analyzed solid cancer mortality among the Hiroshima atomic bomb survivors through Cox regression with time-dependent covariates[2,3] using a model with exposure distance as well as initial radiation dose as explanatory variables[15]. In that analysis, the exposure-distance function as a surrogate for non-initial radiation dose was defined by the following formula with the threshold parameter μ :

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

Here r denotes the ground distance between the location where exposed to the explosion and the hypocenter in Hiroshima. The exposure-distance model had a better fit than the initial-radiation model to the excess relative risk of solid cancer mortality, and the risk increased only in the neighborhood of the hypocenter (within 1.2 km).

The objective of the present study was to examine whether the sex- and age-ATB-specific HD disease mortality among Hiroshima A-bomb survivors can be explained solely through initial radiation dose or not, and to assist in estimating the HD risk among *hibakusha* precisely. We analyzed the HD mortality with the exposure-distance model using $D^*(r \mid \mu)$ defined by (1) as well as the initial radiation model, and compared their performance.

MATERIALS AND METHODS

Subjects

In Hiroshima University, a cohort study of the Hiroshima Atomic Bomb Survivors (ABS) has been conducted since 1968[12]. We chose for analysis 29605 subjects from the ABS who satisfied the following conditions: (i) alive and recognized as an atomic bomb survivor as of January 1, 1970, (ii) having an estimate of initial radiation dose, and (iii) exposed within 3500 m of the hypocenter. These subjects were followed until December 31, 2010. The endpoint was death from HD. Death information including cause of death was obtained from the Vital Statistics Death Schedules, which are based on official death certificates. Tables 1.1 and 1.2 show the sex-specific numbers of subjects categorized by age ATB and exposure distance, respectively.

Radiation dosimetry

To quantify the effect of initial radiation dose in Sieverts (Sv) on the human body, we used the absorbed dose in red bone marrow from neutrons and gamma rays in Gray (Gy) estimated using the Atomic Bomb Survivor 1993 Dose (ABS93D)[7]. The radiation dose calculated with ABS93D is based on the initial radiation only, as is DS86, and ignores residual radiation[21]. The extent of overlap between survivors in the ABS and the LSS was examined by Hayakawa et al in which it was shown that dose estimates of the ABS were close to those of the LSS among the overlapping subjects[6]. However, it has not been investigated the consistency of the ABS93D and DS02, yet.

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

(Males)

age ATB	number of subjects	number of HD deaths	number of censored cases†† (surviving cases††)
[0, 10)	3401	78	3323 (1985)
[10, 20)	2835	150	2685 (1283)
[20, 30)	1122	141	981 (154)
[30, 40)	1654	256	1398 (25)
[40, 50)	1660	313	1347 (0)
[50, 60)	640	119	521 (0)
[60, 80)	66	16	50 (0)
total	11378	1073	10305 (3447)

(Females)

age ATB	number of subjects	number of HD deaths	number of censored cases†† (surviving cases††)
[0, 10)	3208	30	3178 (2180)
[10, 20)	3657	129	3528 (2306)
[20, 30)	3669	363	3306 (1352)
[30, 40)	3656	728	2928 (190)
[40, 50)	2870	622	2248 (4)
[50, 60)	1011	240	771 (0)
[60, 80)	156	33	123 (0)
total	18227	2145	16082 (6032)

†Numbers of persons who migrated out of Hiroshima prefecture or who died from other causes or who were alive as of 31 Dec 2010.

††Number of persons alive as of 31 Dec 2010.

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

(Males)

distance (km)	number of subjects	number of HD deaths	number of censored cases†† (surviving cases††)
[0.0, 0.8)	4	1	3 (0)
[0.8, 1.0)	153	26	127 (20)
[1.0, 1.2)	449	40	409 (110)
[1.2, 1.4)	932	88	844 (249)
[1.4, 1.6)	1232	109	1123 (385)
[1.6, 1.8)	950	112	838 (266)
[1.8, 2.0)	667	64	603 (196)
[2.0, 2.5)	1054	88	966 (301)
[2.5, 3.0)	3866	359	3507 (1274)
[3.0, 3.5)	2071	186	1885 (646)
total	11378	1073	10305 (3447)

(Females)

distance (km)	number of subjects	number of HD deaths	number of censored cases†† (surviving cases††)
[0.0, 0.8)	7	1	6 (3)
[0.8, 1.0)	261	28	233 (48)
[1.0, 1.2)	891	97	794 (231)
[1.2, 1.4)	1737	249	1488 (498)
[1.4, 1.6)	2398	298	2100 (698)
[1.6, 1.8)	1717	218	1499 (556)
[1.8, 2.0)	1078	133	945 (345)
[2.0, 2.5)	1343	162	1181 (465)
[2.5, 3.0)	5369	610	4759 (1996)
[3.0, 3.5]	3426	349	3077 (1192)
total	18227	2145	16082 (6032)

†Numbers of persons who migrated out of Hiroshima prefecture or who died from other causes or who were alive as of 31 Dec 2010.
††Number of persons alive as of 31 Dec 2010.

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

(Males)

dose(Sv)	number of subjects	number of HD deaths	number of censored cases†† (surviving cases††)
[0.00, 0.01)	6739	612	6127 (2158)
[0.01, 0.05)	664	63	601 (158)
[0.05, 0.1)	719	76	643 (225)
[0.1, 0.2)	945	97	848 (275)
[0.2, 0.4)	1005	95	910 (289)
[0.4, 0.6)	386	36	350 (121)
[0.6, 0.8)	247	22	225 (65)
[0.8, 1.0)	182	19	163 (38)
[1.0, 1.5)	190	17	173 (56)
[1.5, 2.0)	109	7	102 (25)
[2.0, 6.0)	192	29	163 (37)
total	11378	1073	10305 (3447)

(Females)

dose(Sv)	number of subjects	number of HD deaths	number of censored cases†† (surviving cases††)
[0.00, 0.01)	9687	1063	8624 (3519)
[0.01, 0.05)	1148	152	996 (352)
[0.05, 0.1)	1313	152	1161 (417)
[0.1, 0.2)	1799	256	1543 (527)
[0.2, 0.4)	1894	228	1666 (540)
[0.4, 0.6)	753	109	644 (242)
[0.6, 0.8)	437	45	392 (138)
[0.8, 1.0)	387	64	323 (85)
[1.0, 1.5)	332	33	299 (94)
[1.5, 2.0)	166	10	156 (52)
[2.0, 6.0)	311	33	278 (66)
total	18227	2145	16082 (6032)

†Numbers of persons who migrated out of Hiroshima prefecture or who died from other causes or who were alive as of 31 Dec 2010.
††Number of persons alive as of 31 Dec 2010.

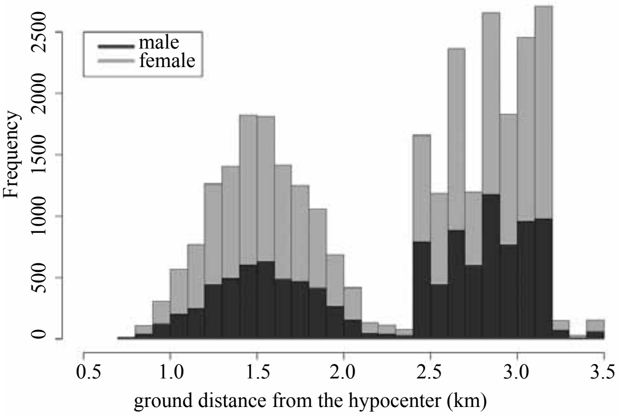

Fig. 1. Histogram of sex-specific numbers of subjects by exposure distance (km) from the hypocenter.

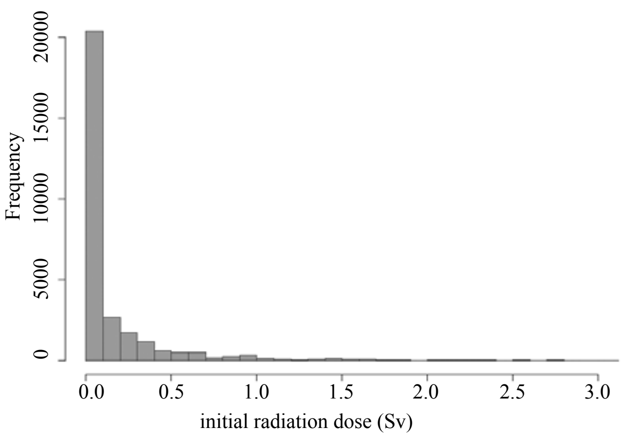

Fig. 2. Histogram of numbers of subjects in the cohort study by initial radiation dose (Sv)

Table 1.3 shows the sex-specific numbers of subjects by categories of initial radiation dose. Histograms of exposure distance and of initial radiation dose are given in Fig. 1 and Fig. 2, respectively. Since we have detailed information about A-bomb survivors' shielding conditions within an exposure distance of 2.0 km, a sufficient number of such subjects were obtained. In cases of an exposure distance beyond 2.5 km, we can assume that their initial radiation doses were zero. However, in the case of an exposure distance between 2.0 km to 2.5 km, only a limited number of samples were available because of the difficulty of estimating the ini-

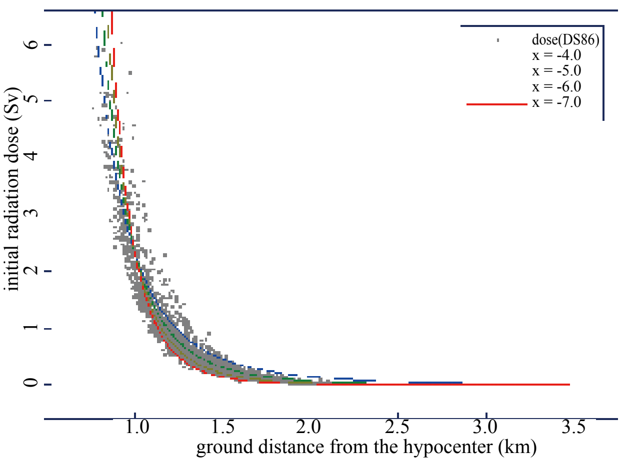

Fig. 3. Scatterplot of individual initial radiation dose versus exposure distance

tial radiation dose. Figure 3 shows the relationship between subjects' initial radiation dose and exposure distance, with fitted curves $f(r \mid x) = 2.3 \times r^x$ based on a power function of exposure distance. It is shown that plots for many subjects are located briefly around the dose-distance curves of $f(r \mid -4)$ to $f(r \mid -7)$.

Statistical analysis

Based on epidemiological evidence that HD mortality risk increases exponentially with age[5,17], we assumed that the hazard function of attained age t for a person exposed to an initial radiation dose D at age a can be expressed as

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

where β_a is the regression coefficient for the effect of the initial dose among Hiroshima *hibakusha* who were age a at the time of exposure, while $g(t, y)$ is a logarithmic function of attained age (t) and calendar year (y) for HD mortality risk in all of Japan during the period 1970 to 2010, which is specified approximately by a sextic polynomial equation of t and y. The parameter δ expresses the logarithm of the background relative mortality from HD for Hiroshima *hibakusha* compared with the whole of Japan. The cohort data were stratified by sex and age ATB into eight strata -- 0-9 years (male/female), 10-19 years (male/female), 20-29 years (male/female), and 30 years and over (male/female) -- and the unknown coefficient parameter (β_a) for each stratum was estimated by applying Cox regression analysis with time-dependent covariates[2,3]. To collect information on weight and factors such as smoking and alcohol consumption was not feasible because it would require enormous expense. We noted RERF's report showing that the influence of non-radiation risk factors such as excessive weight, smoking, alcohol consumption and diabetes were significantly low among atomic bomb survivors in Hiroshima and Nagasaki[24], and also that LSS did not deal with these factors in the risk analysis. We also analyzed in a similar way the exposure-distance dependency based on the function $D^*(r \mid \mu)$ of exposure distance r defined by (1), in which the threshold parameter μ was estimated by applying the optim function[22]. The model using the exposure distance is expressed as follows: $h(t \mid D^*, a) = \exp\left(g(t, t-a+1945)\right) \cdot \exp\left(\delta + \beta_a D^*\right)$. We used the freeware R (version 3.0.0) to implement the numerical-analyses.

RESULTS

Results of the Cox regression analyses of HD death are shown in Tables 2, 3, and 4. Table 2 shows AIC[1] expressing the goodness of fits of the initial dose model (dose), the exposure-distance model (dist) and a model (null) showing neither dose nor the exposure-distance variables by sex and ATB group. Table 2 also shows the difference in AIC of each model compared to the initial radiation dose model. In males, the null model attained the minimum AIC for ATB 10-19, whereas the exposure-distance model had the minimum AIC for the other ATB groups. In females, the exposure-distance model attained the minimum AIC for ATB 30 and over, whereas the null model had the minimum AIC for the other ATB groups. In no case was the initial-dose model optimal in terms of minimum AIC. Table 3.1 shows the estimated coefficients of the dose effect and its 95% CI bounds for each sex-ATB group, and Table 3.2 shows those of the exposure-distance dependency. From these tables, it was found that the effect of initial dose in males was detected only for the 0-9 age ATB group, whereas large effects of exposure distance were estimated for all age ATB groups except the 10-19 group. On the other hand, in females, the effects of neither initial radiation dose nor exposure distance were significant for any age ATB group except 30 and over. Table 4 shows the optimized values of the threshold parameters in the exposure-distance model. It suggests that in

Table 2. AIC values of candidate models and difference in AIC between the initial-dose and other models. The number of parameters in the dose model, distance model and null model are 1, 2 and 0, respectively.

	age ATB	**dose**$^{(a)}$	**dist**$^{(b)}$	**null**$^{(c)}$	**Δdist**†	**Δnull**††
Males	[0, 10)	1186.82	1185.98	1189.19	-0.84	3.21
	[10, 20)	2236.90	2237.50	2235.49	0.60	-2.01
	[20, 30)	1729.70	1729.29	1730.32	-0.41	1.03
	[30 over)	9909.86	9908.56	9909.90	-1.30	1.33
Females	[0, 10)	461.88	463.91	459.91	2.03	-3.99
	[10, 20)	1997.44	1999.52	1995.54	2.08	-3.98
	[20, 30)	5479.04	5480.42	5478.20	1.38	-2.22
	[30 over)	25559.24	25558.56	25558.98	-0.68	0.42

$^{\dagger}(b)-(a)$: The difference in AIC between initial-dose model and distance-function model

$^{\dagger\dagger}(c)-(a)$: The difference in AIC between initial-dose model and null model

Table 3.1. Estimated coefficient (***β***) of the dose effect and its 95% CI

	age ATB	coef.	lower.95	upper.95	p-value
Males	[0, 10)	0.383*	0.079	0.688	0.014
	[10, 20)	0.133	-0.187	0.452	0.416
	[20, 30)	0.262・	-0.026	0.550	0.075
	[30 over)	0.114	-0.036	0.263	0.136
Females	[0, 10)	0.076	-0.695	0.847	0.847
	[10, 20)	0.059	-0.305	0.422	0.752
	[20, 30)	-0.131	-0.380	0.119	0.305
	[30 over)	0.072	-0.032	0.176	0.175

*: 0.01 ≦ p <0.05, ・: 0.05 ≦ p < 0.1

Table 3.2. Estimated coefficient (***β***) of the exposure-distance dependency and its 95% CI

	age ATB	coef.	lower.95	upper.95	p-value
Males	[0, 10)	0.698**	0.318	1.077	0.000
	[10, 20)	0.429	-0.090	0.948	0.105
	[20, 30)	0.625*	0.100	1.149	0.020
	[30 over)	0.236**	0.058	0.413	0.009
Females	[0, 10)	0.066	-1.694	1.826	0.941
	[10, 20)	0.053	-0.727	0.832	0.894
	[20, 30)	-0.308	-0.773	0.158	0.195
	[30 over)	0.225*	0.021	0.430	0.031

**: p < 0.01, *: 0.01 ≦ p <0.05

Table 4. Estimated threshold parameter (***μ***) and its 95% CI

	age ATB	estimate	lower.95	upper.95
Males	[0, 10)	1.05	1.00	1.11
	[10, 20)	1.09	–†	–
	[20, 30)	2.00	1.76	2.24
	[30 over)	1.06	1.01	1.10
Females	[0, 10)	1.50	–	–
	[10, 20)	1.48	–	–
	[20, 30)	1.56	–	–
	[30 over)	1.47	1.37	1.57

† The finite confidence bound was not available because of the non-statistical significance of the corresponding effect of exposure-distance effect. (See. Table 3.2)

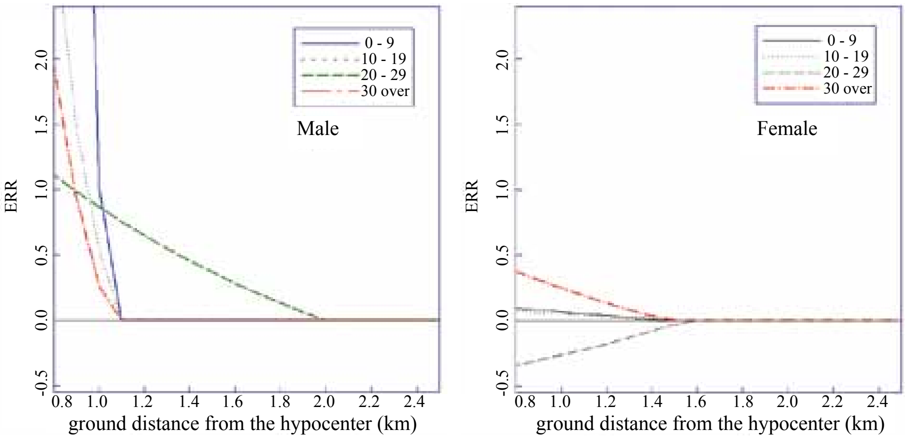

Fig. 4. Fitted exposure-distance dependencies of excess relative risk by sex and age ATB. The colored curves show statistically significant trends.

males the risk became high within about 1.1 km from the hypocenter for all ATB groups except 20-29. Figure 4 shows the fitted exposure-distance dependency of the excess relative risk by sex and age ATB. It indicates that the estimated risk is high for males in the case of being exposed at or near the hypocenter, but no corresponding excess risk can be seen for females.

We also considered fitting a linear-quadratic model of initial radiation dose to our analysis, but the goodness of the fit deteriorated compared with that of the linear initial radiation dose model described above.

DISCUSSION

Several studies have reported the effects of radiation on HD mortality. Ivanov et al analyzed data on the Chernobyl emergency workers and showed that the excess relative risk of ischemic heart disease was 0.41 per Gy[8]. Shimizu et al reported that the sex-averaged excess relative risk per Gy of HD mortality was 14% among atomic bomb survivors in Hiroshima and Nagasaki for the period 1950-2003, and further showed that the initial radiation dose effect was not significant in the low-dose region below 0.5 Gy[24].

We analyzed the relationship between risk of HD mortality and initial radiation dose as well as the exposure distance. It is 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. This suggests that dose due to residual radiation should depend on sex and age ATB. Due to these reasons, we stratified the *hiba-*

kusha cohort data according to sex and age ATB to analyze the effect of exposure to radiation. Table 1.2 shows that the number of deaths within 1.2 km was 193 (6.0%) and that of deaths within 2.0 km was 1464 (45.5%). Table 1.3 shows that the number of deaths in under 0.1 Sv was 2118 (65.8%).

We found a large sex difference in the estimated dose-response relationship: significant excess mortality risk of HD was detected for males who were exposed at ages younger than 10 years whereas almost no excess risk was seen for females. A clearer sex difference was found in the relationship between HD mortality risk and exposure distance, which suggests that the dose due to residual radiation was higher for males than females. Although the estimated effects of initial radiation dose and exposure distance in our cohort study were not adjusted for recognized risk factors such as excessive weight, hypercholesterolemia, smoking, alcohol consumption, and others, it may be concluded that there were some risk factors for HD mortality unique to male survivors who were exposed at a short distance from the hypocenter. For example, it is possible that the effects of radioactive particulate materials with short half-lives that were generated just after the explosion, such as[28] Al, affected only short-distance survivors[16]. However, following that reasoning it is difficult to explain why a corresponding excess risk was not found among female survivors. For this sex difference it may be that although non-initial radiation was the main exposure factor, the risk was abated by female sex hormones present in young age ATB females that are not present in males or older age ATB females. Cui et al reported that early menopause is associated with an increased risk of mortality from coronary heart disease (CHD), which can be explained by a protective effect of endogenous estrogen on the development of atherosclerosis[4]. As possible factors other than initial radiation dose or radioactive particulate materials, malnutrition or mental stress caused by the collapse of family due to the devastation might have elevated HD mortality risk among the atomic bomb survivors. Kubzansky and Kawachi showed that negative emotions influence the development of CHD[10]. Shirai et al also reported that men with low perceived enjoyment of life had an increased risk of mortality from CHD and other cardiovascular diseases[25]. Young males might therefore be more sensitive to health deterioration from the collapse of family.

One cause of the complex sex and age ATB- dependency in the dose-response relationship may be the limited follow-up period of our study, which started in 1970. We disregard early effects of exposure to the atomic bomb, such as acute death from the blast and acute radiation sickness, as well as late effects due to malignant tumors etc., which might reduce the observed excess mortality from HD through the competing risk effect. Preston et al showed that the corresponding estimated time-averaged excess relative risks at 1 Sv were 9.1, 3.3 and 6.2 for acute lymphoid leukemia, acute myelogenous leukemia, and chronic myelogenous leukemia, respectively[20]. Matsuura et al showed that the relative risk of leukemia at 1 Gy of bone marrow dose was 2.37, and significantly higher risks were observed for all cancers other than leukemia among survivors who survived for 20 years or more after the bombing[12]. Ozasa et al reported that the sex-averaged excess relative risk per Gy was 0.42 for all solid cancer at age 70 after exposure at age 30, and that the sensitivity was about two times higher in females than in males[19]. We need further investigation into sex and age ATB differences in HD mortality among the atomic bomb survivors.

CONCLUSION

We analyzed HD mortality risk among Hiroshima *hibakusha* using Cox regression analysis. The results suggest that initial radiation dose was not the major risk factor. Some unknown risk factor elevated HD mortality among male Hiroshima *hibakusha*, who were exposed near the hypocenter, while the risk was reduced in females who were exposed at young ages ATB.

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We declare that we have no conflict of interest.

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