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Source: Radiation Research, 176(6) : 787-795

Published By: Radiation Research Society

URL: https://doi.org/10.1667/RR2676.1

RADIATION RESEARCH **176**, 787–795 (2011)
0033-7587/11 $15.00

DOI: 10.1667/RR2676.1

Effect of Radiation on Age at Menopause among Atomic Bomb Survivors

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Sakata, R., Shimizu, Y., Soda, M., Yamada, M., Hsu, W-L., Hayashi, M., Ozasa, K. Effect of Radiation on Age at Menopause among Atomic Bomb Survivors. *Radiat. Res*. 176, 787–795 (2011).

Exposure to ionizing radiation has been thought to induce ovarian failure and premature menopause. Proximally exposed female atomic bomb survivors were reported to experience menopause immediately after the exposure more often than those who were distally exposed. However, it remains unclear whether such effects were caused by physical injury and psychological trauma or by direct effects of radiation on the ovaries. The objective of this study was to see if there are any late health effects associated with the exposure to atomic bomb radiation in terms of age at menopause in a cohort of 21,259 Life Span Study female A-bomb survivors. Excess absolute rates (EAR) of natural and artificial menopause were estimated using Poisson regression. A linear threshold model with a knot at 0.40 Gy [95% confidence interval (CI): 0.13, 0.62] was the best fit for a dose response of natural menopause (EAR at 1 Gy at age of 50 years = 19.4/1,000 person-years, 95% CI: 10.4, 30.8) and a linear threshold model with a knot at 0.22 Gy (95% CI: 0.14, 0.34) was the best fit for artificial menopause (EAR at 1 Gy at age of 50 years for females who were exposed at age of 20 years = 14.5/1,000 person-years, 95% CI: 10.2, 20.1). Effect modification by attained age indicated that EARs peaked around 50 years of age for both natural and artificial menopause. Although effect modification by age at exposure was not significant for natural menopause, the EAR for artificial menopause tended to be larger in females exposed at young ages. On the cumulative incidence curve of natural menopause, the median age at menopause was 0.3 years younger in females exposed to radiation of 1 Gy compared with unexposed females. The median age was 1 year younger for combined natural and artificial menopause in the same comparison. In conclusion, age at menopause was thought to decrease with increasing radiation dose for both natural and artificial menopause occurring at least 5 years after the exposure.

INTRODUCTION

Exposure to ionizing radiation has been thought to induce ovarian failure and premature menopause based on the follow-up of female patients who underwent radiotherapy (*1–5*). Since most of those effects were observed in patients with high-dose radiotherapy, the effects of low-dose radiation are still unclear. The atomic bomb (A-bomb) survivors were exposed to relatively low doses of radiation compared to those in the radiotherapy studies. An early study showed that the proportion of female A-bomb survivors who experienced menopause immediately after the exposure was significantly larger in the proximal exposure group compared to the distal exposure group, with average menopausal age being significantly younger, particularly among those with acute radiation syndromes (*6*). However, it remains speculative whether the younger menopausal age is caused by physical injury or psychological trauma due to their experiences in the bombing and bad health conditions after that or by effects of radiation on ovarian function.

Menopause is classified as either natural or artificial. The former is caused by spontaneous loss of ovarian function. Early natural menopause has been associated with increased risks of osteoporosis (*7*) and cardiovascular diseases (*8*) as well as with a higher mortality from all causes (*9*). Thus early natural menopause serves as an additional health risk among elderly females. Artificial menopause is caused mainly by artificial loss of ovarian function by bilateral oophorectomy and hysterectomy with unilateral oophorectomy and sometimes by intensive radiotherapy and chemotherapy against cancers of the uterus and ovary (*10*).

Investigation of the association of exposure to A-bomb radiation and early natural menopause that occurred long after the exposure is important to evaluate the late health effects of radiation exposure on ovarian function at relatively low dose levels compared with those after radiotherapy. It is also important to investigate artificial menopause in the female A-bomb survivors because ovarian and uterine corpus cancers have increased among them (*11*) and often lead to oophorectomy and abdominal radiation therapy and the induction of artificial menopause. Investigations limited to natural menopause were thought to underestimate the overall effects of A-bomb radiation on menopause. Therefore, we investigated the age at natural and artificial menopause occurring at least 5 years after the

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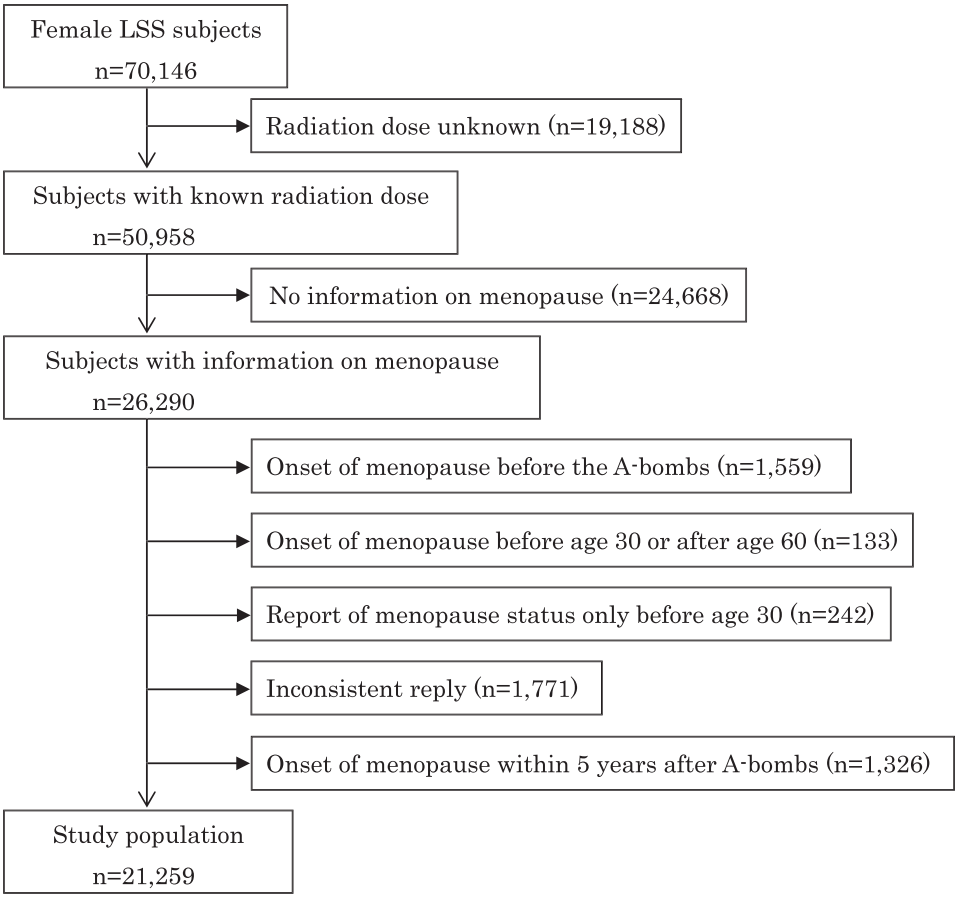

FIG. 1. Breakdown of the study population.

radiation exposure in the Life Span Study (LSS) population of the Radiation Effects Research Foundation (RERF).

SUBJECTS AND METHODS

Study Population

The LSS is a longitudinal cohort study consisting of 50,175 males and 70,146 females who either were exposed to the atomic bombings in Hiroshima or Nagasaki or were nonexposed (Fig. 1). Follow-up of the cohort was initiated in 1950 by the Atomic Bomb Casualty Commission and then carried on by RERF (*12*). RERF conducted three mail surveys (1969, 1978 and 1991) on the female subjects in the LSS population. Among 50,958 females with known radiation dose in the LSS, 26,290 subjects replied to the question about menopause in one of the three surveys. In the mail survey questionnaires, age at menopause was asked about in the following manner without any detailed information (underlined blanks to be filled in with age information): ''Age at menopause was _____ years'' in the 1969 mail survey, and ''How old were you when your menstrual periods stopped? _____ years of age'' in the 1978 and 1991 mail surveys. The subject's age at menopause was determined by the reply to the question about age at menopause in the earliest mail survey. The subjects reporting that they had not experienced menopause in the latest mail survey were treated as censored subjects at their ages at that time. In the 1978 and 1991 surveys, the questionnaires asked about menopause separately by natural or artificial category, but this was not asked in the 1969 survey. Cessation of menses caused by hysterectomy is not menopause by medical definition if ovarian function remains. However, most people assume cessation of menses is menopause regardless of cause. Since detailed information on the cause of menopause was not obtained in the questionnaires, we defined cessation of menses after hysterectomy and other gynecological surgeries as artificial menopause.

The population at risk in this study was the female LSS subjects who were between 30 and 60 years of age and did not experience menopause because this age range is assumed to include the potential for menopause. The subjects who reported the following were excluded from the analysis: (1) onset of menopause before the A-bomb exposure (1,559 subjects); (2) age at menopause of 30 years or younger or of 60 years or older (133 subjects); (3) those who reported menopause status only in the mail survey

TABLE 1
Number of Female Subjects Included in This Study from the Life Span Study (LSS) Cohort by City and Dose Categories

Weighted ovarian dose (Gy)	Subjects of this study	
	Hiroshima (%[a])	Nagasaki (%[a])
<0.005	5,624 (43)	3,602 (37)
≥0.005, <0.5	8,494 (44)	2,432 (43)
≥0.5, <1.0	483 (36)	241 (40)
≥1.0, <1.5	133 (32)	87 (36)
≥1.5	110 (28)	53 (36)
Total	14,844 (43)	6,415 (39)

[a] Percentage of females in the whole LSS cohort by city and dose categories.

before the age of 30 and did not respond to subsequent mail surveys (242 subjects); and (4) inconsistent replies, e.g., natural menopause with history of uterine or ovarian cancer, or premenopausal status when older than 60 at the time of the mail survey (1,771 subjects). In addition, the subjects who experienced menopause within 5 years after A-bomb exposure were excluded from the analyses in an effort to exclude the potential effects of physical injury and psychological trauma after A-bomb exposure (1,326 subjects). Consequently, the study population consisted of 21,259 females, 42% of the target population. The distribution of the subjects by city and dose category is shown in Table 1.

Subjects were included in the observation at age 30 years and reached the end point at age of menopause (for both natural and artificial) or were treated as censored at age at the latest mail survey that reported premenopausal status (the age had to be younger than 60 years due to the exclusion criteria). If a subject reported being premenopausal in a specific mail survey and did not report the age of menopause in the later mail surveys, she was treated as censored at the age at the specific mail survey. In the analysis for natural menopause, subjects who experienced artificial menopause were treated as censored at the age of artificial menopause, and in the analysis for artificial menopause, subjects who experienced natural menopause were censored in the same way at that age.

Radiation and Other Risk Factors

Radiation doses for the ovary have been estimated based on information regarding individual location and shielding status at the time of the bombings in terms of γ-ray dose and neutron dose using the Dosimetry System 2002 (DS02) (*13*). Individual weighted ovarian doses were calculated as the sum of γ-ray dose plus 10 times the neutron dose.

Information on parity, smoking status and age at menarche was obtained from the mail surveys. Parity was categorized as parous and nulliparous; the former was defined as experience of delivery based on the replies to the questions about age at first delivery, number of children, number of deliveries, and other relevant information in any one of the three surveys. Age at menarche was determined as the age at menarche informed by the earliest available survey. Ever-smoker was defined as the subject who was a smoker or ex-smoker at the mail survey that determined her age at menopause, and nonsmoker was defined in the same manner. For censored subjects, smoking status was determined by the latest available survey. When any information was not available for parity, age at menarche, or smoking, the value was treated as missing.

Statistical Analysis

Poisson regression was used to estimate the excess absolute rates (EAR) for onset of menopause associated with weighted ovarian dose (d) effects. EAR indicates the number of excess outcomes per unit person-years and is thought to be the most appropriate measure of risk because background rates for menopause are very irregular with the attained age, i.e., extremely high at nearly 50 years of age. The EAR model we used was

$$\lambda_0(c,b,p,s,m,a) + \rho(d)\varepsilon(a,e),$$

where the variables are city (c), birth year (b), parity (p), smoking status (s), age at menarche (m), attained age (a), radiation dose (d) and age at exposure (e) (*14*).

The function of $\lambda_0(c,b,p,s,m,a)$ described the background incidence rate of menopause. We considered interaction between attained age and other factors in the background rate function. The function $\rho(d)$ represents dose response. The following dose–response models were compared for model fit:

$$\begin{aligned} &\rho(d) = \beta d && \text{Linear (L)}\\ &\rho(d) = \beta d + \gamma d^2 && \text{Linear-quadratic (LQ)}\\ &\rho(d) = \gamma d^2 && \text{Quadratic (Q)} \end{aligned}$$

$$\begin{cases} \beta(d-\tau)\, d > \tau & d > \tau \\ 0 & d \le \tau \end{cases} \qquad \text{Linear threshold (LT)}$$

τ is a threshold dose, which was examined for a wide range of possible values by stepping up by 0.01 Gy. The function of $\varepsilon(a,e)$ was assumed as effect modification on EAR by attained age (a) and age at exposure (e). First, the best-fitting function was determined among the four models, and significance of effect modification by attained age and age at exposure was tested on the selected model. After that the best-fitting model was determined again among the four models with the effect modification term. We used the Akaike Information Criteria (AIC) for comparison of model fitting. Significance tests of improvement in model fit between nested models were based on likelihood ratio tests.

Onset of menopause and time at risk in terms of person-years were tabulated by age at exposure (5-year categories for ages 0 through 39 and 40 or higher), attained age (5-year intervals for ages 30 through 60), birth cohort (10 categories with 5-year intervals for 1894 through 1939 and 1940 or

TABLE 2
Distribution of Subjects and Mean Age at Menopause by Available Covariates

	Natural menopause			Artificial menopause			Censored		
Categories	n^a	Age^b	P^c	n^a	Age^b	P^c	n^a		Total
City									
Hiroshima	11,657	49.5	0.80	1,661	43.7	0.02	1,526		14,844
Nagasaki	4,864	49.5		747	43.2		804		6,415
Birth cohort									
1894–1905	1,105	50.9	<0.001	19	50.5	<0.001	0		1,124
1906–1925	9,056	49.3		857	44.5		51		9,964
1926–1945	6,360	49.6		1,532	43.0		2,279		10,171
Parity									
Parous	14,078	49.6	<0.001	1,934	43.8	<0.001	2,035		18,047
Nulliparous	1,362	49.1		285	42.7		160		1,807
Missing	1,081	49.3		189	42.6		135		1,405
Smoking status									
Never smoker	13,206	49.7	<0.01	1,888	43.7	0.06	1,954		17,048
Ever smoker	2,820	49.0		482	43.1		342		3,644
Missing	495	49.5		38	44.1		34		567
Age at menarche									
<5	5,296	49.6	0.57	977	43.6	0.18	1,220		7,493
15, 16	5,351	49.5		708	43.8		432		6,491
>17	2,507	49.5		261	43.3		91		2,859
Missing	3,367	49.6		462	43.3		587		4,416
Total	16,521	(78%)		2,408	(11%)		2,330	(11%)	21,259

[a] Number of females.
[b] Mean age at menopause.
[c] P for test of independence.

later), radiation dose (0.005, 0.02, 0.04, 0.06, 0.08, 0.1, 0.125, 0.15, 0.175, 0.2, 0.25, 0.3, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5 and 3 Gy), city (Hiroshima and Nagasaki), parity (parous, nulliparous and missing), smoking history (never, ever and missing), and age at menarche (age 14 or younger, 15 or 16, 17 or older, and missing). The cell-specific mean values are also included for radiation dose and each age/time variable. Statistical analyses were carried out using the AMFIT program of Epicure software (*15*).

Cumulative Incidence Curves of Menopause

Cumulative incidence curves of menopause were illustrated based on the best-fitting models. The incidence rate of combined natural and artificial menopause at a given age was the sum of them, each of which was calculated separately based on the best-fitting model. The numbers of females who were expected to reach menopause at a given age were calculated by multiplying the number of premenopausal subjects by the incidence rate of menopause at that age. Then the cumulative incidence of menopause was estimated under the condition of being exposed in Hiroshima, born in 1925, parous, experiencing menarche at age 15 or 16 years, and never smoking.

RESULTS

Among the eligible of 21,259 subjects, 16,521 reported that they had experienced natural menopause and 2,408 reported artificial menopause. The other 2,330 subjects were censored. Mean ages of menopause by background factor are shown in Table 2. Natural menopause was experienced at younger ages in the subjects who had not experienced childbirth compared with those who had ($P < 0.001$). It was also experienced at younger ages in ever-smokers compared with never-smokers ($P < 0.01$). However, the mean age at natural menopause was not significantly different between the cities and categories of age at menarche. Similar tendencies were observed for artificial menopause, though artificial menopause was experienced at younger ages than natural menopause.

Table 3 shows the mean age at menopause by weighted ovarian dose. Mean age at natural menopause for the subjects with the dose range of 0.005–0.5 Gy appeared to be similar to those with doses under 0.005 Gy and became younger with increasing radiation dose over 0.5 Gy. Mean age at artificial menopause also decreased with increasing dose. Proportions of artificial menopause in the total menopause in a given dose range markedly increased at 0.5 Gy or higher, reaching 40% among the subjects who were exposed to a dose of 1.5 Gy or higher.

The distribution of females who experienced natural menopause before age 45 by weighted ovarian dose is shown in Table 4. In the lowest dose category, 7% of females experienced menopause before age 45, the percentage increased with dose, and 19% of females experienced menopause before age 45 in the highest dose category in

TABLE 3
Mean Age at Menopause by Weighted Ovarian Dose Categories

Weighted ovarian dose (Gy)	N^a	Natural menopause			Artificial menopause		
		n^b	(%[c])	Mean age[d]	n^b	(%[c])	Mean age[d]
<0.005	9,226	7,231	(88)	49.6 ± 3.4	972	(12)	43.7 ± 5.1
≥0.005, <0.5	10,926	8,475	(88)	49.5 ± 3.4	1,204	(12)	43.6 ± 5.3
≥0.5, <1.0	724	561	(82)	49.2 ± 3.3	120	(18)	42.9 ± 4.8
≥1.0, <1.5	220	156	(77)	48.9 ± 3.7	47	(23)	42.7 ± 5.7
≥1.5	163	98	(60)	47.9 ± 4.2	65	(40)	41.7 ± 5.2
				$P^e < 0.0001$			$P^e = 0.0135$
Total	21,259	16,521	(87)	49.5 ± 3.4	2,408	(13)	43.6 ± 5.2

[a] Number of females by dose category including censored females.
[b] Number of females experiencing natural (or artificial) menopause by dose category.
[c] Percentage experiencing natural (or artificial) menopause in total menopause.
[d] Mean age at menopause.
[e] P for trend.

which females received 1.5 Gy or more (mean dose 2 Gy). The probability of experiencing natural menopause before age 45 increased significantly with dose ($P < 0.001$).

Table 5 shows results of Poisson regression analysis. Since birth cohort, parity, smoking status and age at menarche had significant interactions with attained age in the background rate function [$\lambda_0(c,b,p,s,m,a)$], those interaction terms were included in the function of the model for natural menopause as well as main effects.

For natural menopause, the LT model with effect modification by attained age was the model with the best fit (EAR at 1 Gy at age of 50 years = 19.4/1,000 person-years, 95% CI: 10.4, 30.8). The threshold was estimated to be 0.40 Gy (95% CI: 0.13, 0.62). EAR for natural menopause peaked at 50 years of age, which was expressed by a significant effect modification by attained age [ln(age/50)^2, $P < 0.001$]. The effect modification by age at exposure was not statistically significant ($P = 0.19$). The shape of the dose response and EAR estimates for categorized dose are shown in Fig. 2. The model ultimately selected for natural menopause was

TABLE 4
Distribution of Natural Menopause Experienced before Age 45 by Ovarian Dose Categories

Weighted ovarian dose (Gy)	Mean dose (Gy)	Age at natural menopause			
		<45 years		≥45 years	
		n^a	(%[b])	n^a	(%[b])
<0.005	0.001	477	6.6	6,754	93.4
≥0.005, <0.5	0.088	584	6.9	7,891	93.1
≥0.5, <1.0	0.689	43	7.7	518	92.3
≥1.0, <1.5	1.222	18	11.5	138	88.5
≥1.5	1.972	19	19.4	79	80.6
			$P^c < 0.001$		
Total	0.092	1,141		15,380	

[a] Number of females.
[b] Percentage of females in natural menopause.
[c] P for the Cochran-Armitage test.

$$\lambda_0(c,b,p,s,m,a) + 32.3td\exp[-45.58\ln(a/50)^2]$$
$$\begin{cases} td = 0 & \text{if } d \leqq 0.40\,\text{Gy} \\ td = d - 0.40 & \text{if } d > 0.40\,\text{Gy}. \end{cases}$$

The model for artificial menopause was constructed in the same way. Since birth cohort and parity indicated significant interaction with attained age in the background function, these interaction terms were included with main effects.

The parameters for dose response were shown in Table 5. The LT model with effect modification by attained age and age at exposure was the model with the best fit (EAR at 1 Gy at age of 50 years for females who were exposed at age of 20 years = 14.5/1,000 person-years, 95% CI: 10.2, 20.1). The threshold was estimated to be 0.22 Gy (95% CI: 0.14, 0.34). EAR for artificial menopause also peaked at around 50 years of age but was modified by attained age in a different fashion from natural menopause [(age – 50)^2, $P < 0.001$]. The EAR tended to be the largest at age at exposure of 10 years ($P < 0.001$). The dose shape and EAR estimates for categorized doses are shown in Fig. 3. The model selected for artificial menopause was

$$\lambda_0(c,b,p,s,m,a) + 47.4td\exp[-0.005598(a-50)^2 - 0.9356(e-10)^2/100].$$

Cumulative incidence curves of natural menopause were illustrated from the age of 30 to 60 years (Fig. 4). The 25th percentile of age at which the subjects experienced natural menopause was 49.0, 48.2 and 47.7 years for doses of 0–0.40 Gy (under the threshold), 1 Gy and 1.5 Gy, respectively. The median ages were 50.9, 50.4 and 50.1 years, respectively. The difference in age between doses of 0–0.40 Gy and 1.5 Gy decreased (1.3 years at the 25th percentile and 0.8 year at the median). Combined cumulative incidence of both natural and artificial menopause showed a larger difference than natural menopause; median ages of menopause were 50.5, 49.3 and 48.4 years

TABLE 5
Parameter Estimates of the Dose–Response Models for Excess Absolute Rate (EAR) for Natural and Artificial Menopause

	Natural menopause				Artificial menopause			
Model	L[b]	LQ	Q	**LT**	L	LQ	Q	**LT**
b: linear[a]	17.49	8.19	–	**32.27**	28.43	12.1	28.74	**47.36**
g: quadratic	–	7.64	12.99	**–**	–	17.74	–	**–**
t: threshold	–	–	–	**0.40**	–	–	–	**0.22**
Effect modification		–	–	–	–	–	–	**–**
Attained age ($\ln(age/50)^2$)	–44.73	–44.36	–43.85	**–45.58**	–	–	–	**–**
Attained age ($(age - 50)^2$)	–	–	–	**–**	–0.0049	–0.0055	–0.0060	**–0.0056**
Age at exposure ($(atb - 10)^2/100$)	–	–	–	**–**	–0.85	–0.90	–0.93	**–0.94**
Deviance	41147.06	41145.05	41146.28	**41141.70**	16272.85	16258.40	16263.00	**16257.37**
Parameters	26	27	26	**27**	21	22	21	**22**
AIC	41199.06	41199.05	41198.28	**41195.70**	16314.85	16302.40	16305.00	**16301.37**

Note. Bolded columns are the selected model.

[a] The EAR model was defined as $\lambda_0(c,b,p,s,m,a) + \rho(d)\varepsilon(a,e)$ with city (c), birth year (b), parity (p), smoking status (s), age at menarche (m), attained age (a), radiation dose (d) and age at exposure (e). $\rho(d)$ was βd for the linear model, $\beta d + \gamma d^2$ for linear-quadratic model, γd^2 for the quadratic model, $\beta(d - \tau)$ when $d > \tau$ and 0 when $d \leq \tau$ for threshold model included τ as a threshold.

[b] L: linear, LQ: linear-quadratic, Q: quadratic, LT: linear threshold.

for females exposed to radiation doses of 0–0.22 Gy (under the threshold), 1 Gy and 1.5 Gy, respectively.

DISCUSSION

The primary objective of this study is to investigate the association of radiation exposure and age at menopause in female A-bomb survivors, focusing on the possible late health effects of early menopause occurring at least 5 years after the exposure. A significant association between radiation and early menopause occurring 5 years or more after the A-bomb exposure, which excluded early menopause possibly caused by physical injury and psychological trauma immediately after the A-bomb exposure, suggested that radiation effects on ovarian function may cause the early onset of menopause. Although dose-dependent effects of radiotherapy on premature menopause have been described in several previous studies, most of them were carried out on cancer survivors who underwent radiotherapy with extremely high radiation doses such as over 10 Gy (*1–5*). In contrast, radiation doses of A-bomb survivors are relatively low compared to those experienced in such radiotherapy (mean dose among females receiving over 0.005 Gy is 0.2 Gy). This study thus provides new evidence for radiation producing an earlier onset of menopause at lower dose levels.

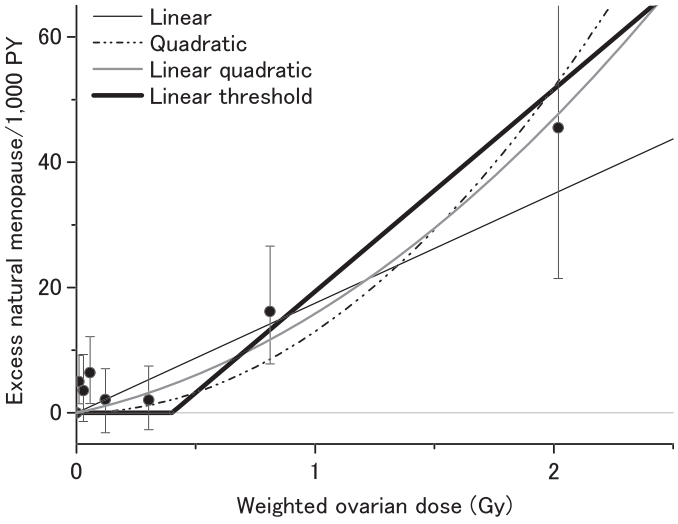

FIG. 2. Variations of excess absolute rate (EAR) of natural menopause by weighted ovarian dose. The graph shows excess rates at age 50; there is no effect modification by age at exposure. The thick solid line is the selected model. The points with error bars are non-parametric estimates.

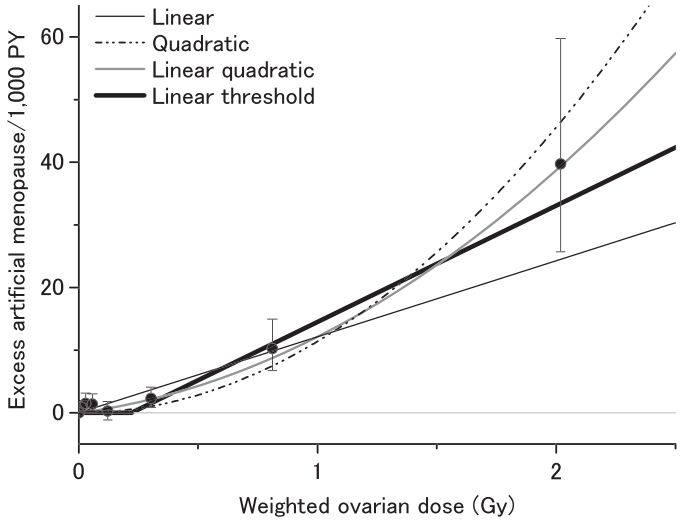

FIG. 3. Variations of excess absolute rate (EAR) of artificial menopause by weighted ovarian dose. The graph of EAR shows excess rates at age 50 for females who were exposed at age 20. The thick solid line is the selected model. The points with error bars are non-parametric estimates.

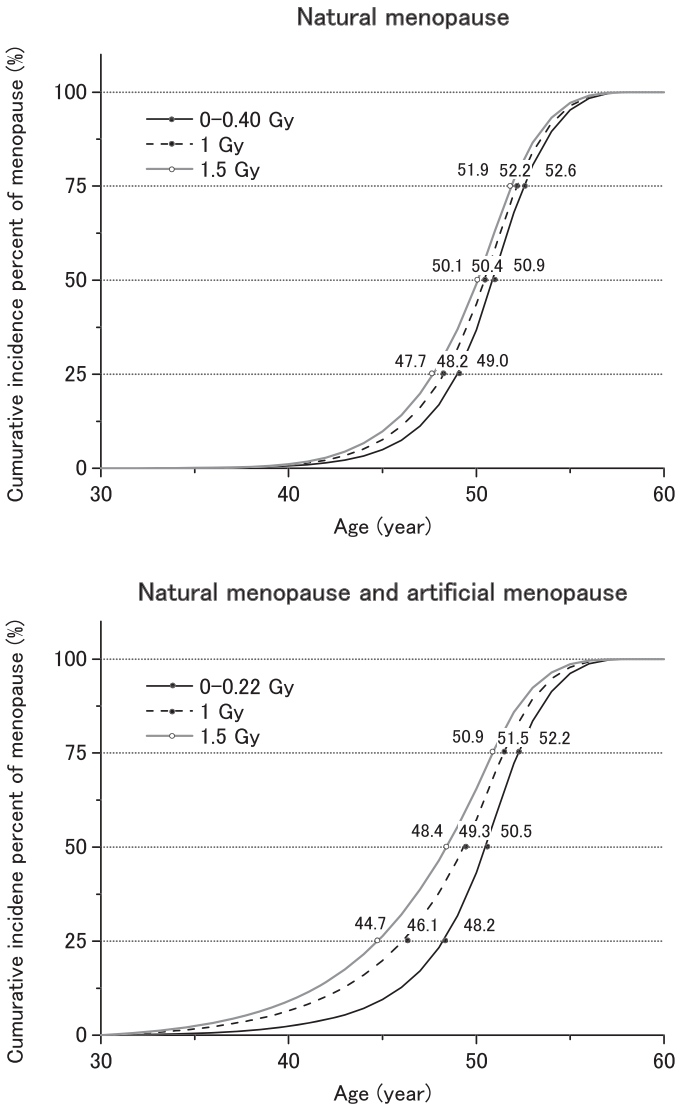

FIG. 4. Cumulative incidence curves of menopause based on the final models. Curves shown are those assumed for females who were exposed in Hiroshima, were born in 1925, were parous, never smoked and experienced menarche at age 15 or 16 years. Ages at the 25th, 50th and 75th percentiles by weighted ovarian dose exposure are shown.

Earlier onset of natural menopause was dose-dependent in female A-bomb survivors in this study. The magnitude was estimated to be an 0.8-year advancement at the median age of natural menopause among those who were exposed to 1.5 Gy. We also found that 20% of females exposed to 1.5 Gy or more experienced natural menopause before age 45. It is difficult to directly compare Table 4 and the cumulative curve in Fig. 4 calculated on the basis of certain females (exposed in Hiroshima, born in 1925, parous, never smoker and age at menarche of 15 or 16 years). However, the two are comparable, with the number of females experiencing menopause before age 45 among females exposed to around 1.5 Gy roughly twice that of females exposed to 0 Gy. Germ cell damage from radiation is thought to be one of the possible causes of ovarian failure and premature menopause (*16, 17*). The human ovary contains a fixed pool of primordial follicles, reaching a maximum quantity at 5 months of gestational age that then declines with increasing age. The mechanism of menopause is yet to be fully explained, but it is thought that when the number of oocytes declines to approximately 1,000, menopause is experienced (*18*). Thus the damage of oocytes by radiation and the consequent decrease in the number of pooled oocytes are thought to hasten menopause.

The dose response of radiation effects on natural menopause was linear with a threshold of 0.40 Gy. Wallace *et al*. reported a model for predicting the age at which ovarian failure is likely to develop after radiation therapy (*19*). The LD_{50} of the human oocyte estimated to be less than 2 Gy (*17*), and therefore radiation exposure of 0.40 Gy is estimated to reduce the number of oocytes by 13%. Although the reduction of oocytes may be sufficient to induce premature menopause according to Wallace's hypothesis, no excess of premature menopause was observed at the level of 0.4 Gy in our study. Their studies were based on high-dose radiation such as in radiotherapy, and they extrapolated the effects to low doses, so a threshold may not have been detectable. On the other hand, such small effects at the level of 0.4 Gy or lower may not have been detected in our study because information on age at menopause was obtained in 1-year units and menopause occurs frequently in a short age range. In addition, uncertain memories and unclear definitions about menopause, discussed later, may reduce the detection power because of nondifferential misclassification. No information is available on the threshold value for killing of human oocytes to our knowledge, but the possibility of biological repair of the damaged follicles has been suggested (*20*).

The number of females experiencing artificial menopause increased with radiation dose, and the age at artificial menopause decreased with dose. Although causes of artificial menopause were not asked for in any of the mail surveys, 43.6% of females experiencing artificial menopause reported a history of myoma in the surveys, 5.2% reported uterine cancer, 1.2% reported ovarian cancer, and 30.7% reported unknown disease of the uterus or ovary. In previous studies on A-bomb survivors, significant associations with radiation were observed for myoma, ovarian cancer and uterine cancer among females who were exposed at young ages (*11, 21*). The increasing prevalence of artificial menopause with increasing radiation dose is thought to be caused by the increasing possibility of hysterectomy or oophrectomy due to such diseases among exposed females.

Ever-smokers compared to never-smokers and nulliparous females compared to parous females tended to experience earlier menopause in this study. Those results were consistent with those observed in some previous analyses of the relationship between lifestyle and age at menopause (*22–27*). The prevalence of ever-smokers and

nulliparous females tended to increase in those with high radiation doses to the ovary (data not shown). Based on the findings, those factors were incorporated into the background function to adjust for them.

Age at menopause of the subjects was determined by self-reports in the mail surveys in this study. Many studies adopted the definition by the World Health Organization (WHO) for natural menopause (*28*). The WHO definition is that ''[n]o menses for 12 consecutive months with no obvious cause (such as pregnancy, lactation) will retrospectively define a women's last menstrual period'' (*29*). Respondents replied to questions about age at menopause in accordance with their own individual definition of menopause, which might not have met the WHO definition. Some females might have replied to the question by considering of the age of permanent cessation of menses, but some might have replied regarding age at amenorrhea without 12 months passing since cessation. There might also have been recall errors, especially for replies long after menopause occurred. However, it is difficult to clarify how respondents defined their menopause experience and how such recall errors were related to radiation dose, if at all.

With respect to reproducibility of age at menopause among the subjects who replied to two mail surveys or more, 70.4% of females reported ages within ± 2 years between the two surveys. There was no tendency for older subjects to report later ages at menopause and vice versa, and the distribution of the differences in age displayed bilateral symmetry (data not shown). That fact suggested a high reproducibility of self-reported age at menopause via mail surveys despite long intervals of about 10 years between the surveys.

Some studies have observed secular trends of age at menopause shifting toward older ages (*30, 31*). However, the eldest birth cohort reported the oldest age at menopause in this study. In the eldest birth cohort in this study, those who experienced menopause before 1950 were excluded from the analysis; i.e., those who experienced menopause at young ages were excluded. In addition, in the recent birth cohorts, many females were not followed up to old ages and may not have reached menopause, and consequently the reported ages at menopause were shifted toward younger ages. Therefore, birth cohort effects in this study did not contradict the previous reports and a similar study should be performed to evaluate birth cohort effects after the entire LSS cohort reaches menopause.

In conclusion, age at menopause decreases with increasing radiation dose among female A-bomb survivors for menopause occurring 5 years or more after the exposure. The radiation effects were significant on natural menopause, which suggested effects of radiation on ovarian function. Effects were also observed in artificial menopause, which might be related to an increasing incidence of myoma and uterine and ovarian cancers, which are known to have a significant relationship to radiation exposure.

ACKNOWLEDGMENTS

The Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan is a private, non-profit foundation funded by the Japanese Ministry of Health, Labour and Welfare (MHLW) and the U.S. Department of Energy (DOE), the latter in part through the National Academy of Sciences. We thank the RERF Master File Section for its hard work in assembling the mail survey information and maintaining the relevant data.

Received: May 16, 2011; accepted September 16, 2011; published online: October 11, 2011

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