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Incidence of Breast Cancer in the Life Span Study of Atomic Bomb Survivors: 1958–2009

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The importance of reproductive history in breast tissue development and etiology of sporadic breast cancer in females is well established. However, there is limited evidence of factors, other than age, that modify risk of radiation-related breast cancer. In this study, we evaluated breast cancer incidence in the Life Span Study cohort of atomic bomb survivors, adding 11 years of follow-up and incorporating reproductive history data. We used Poisson regression models to describe radiation risks and modifying effects of age and reproductive factors. Among 62,534 females, we identified 1,470 breast cancers between 1958 and 2009. Of 397 new cases diagnosed since 1998, 75% were exposed before age 20. We found a strong linear dose response with excess relative risk (ERR) of 1.12 per Gy [95% confidence interval (CI): 0.73 to 1.59] for females at age 70 after exposure at age 30. The ERR decreased with increasing attained age ($P = 0.007$) while excess absolute rate (EAR) increased with attained age up to age 70 ($P < 0.001$). Age at menarche was a strong modifier of the radiation effect: for a given dose, both the ERR and EAR decreased with increasing age at menarche ($P = 0.007$ and $P < 0.001$). Also, independently, age-at-exposure effects on ERR and EAR differed before and after menarche ($P = 0.043$ and $P = 0.015$, respectively, relative to log-linear trends), with highest risks for exposures around menarche. Despite the small number of male breast cancers (n = 10), the data continue to suggest a dose response (ERR per Gy = 5.7; 95% CI: 0.3 to 30.8; $P = 0.018$). Persistently increased risk of female breast cancer after radiation exposure and its modification pattern suggests heightened breast sensitivity during puberty.

Editor's note. The online version of this article (DOI: 10.1667/RR15015.1) contains supplementary information that is available to all authorized users.

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INTRODUCTION

Exposure to ionizing radiation is a well-established risk factor for female breast cancer, particularly when exposure occurs at a young age (*1*). Much of the available evidence derives from the Life Span Study (LSS) of atomic bomb survivors (*2, 3*) and patients exposed to diagnostic or therapeutic radiation for benign conditions (*4, 5*) and cancer (*6, 7*). A pooled analysis of breast cancer and radiation risk by Preston *et al*. (*8*), including the LSS and seven other irradiated cohorts, supported the linearity of radiation dose response and importance of attained age and age at exposure as modifiers of radiation risk both on the excess relative risk (ERR) and excess absolute risk (EAR) scale. However, previous analysis of the LSS breast cancer incidence data (*3*) showed no evidence of an age-at-exposure effect on the ERR, when adjusted for modifying effects of attained age, whereas both attained age and age at exposure had significant independent effects on the EAR.

The importance of reproductive history in breast tissue development and etiology of sporadic breast cancer in females is well established. However, apart from age at exposure and attained age, epidemiological data on modifiers of radiation risk of breast cancer are sparse and inconsistent (*1, 9*). Several studies reported that nulliparity (*10*), family history of breast cancer (*11*), personal history of benign breast disease (*12*), and exposure around the time of menarche (*13, 14*) might increase radiation risk, while others found no evidence of significant effect modification (*15, 16*). The LSS cohort of atomic bomb survivors, with a broad range of risk factor data collected over several mail surveys and clinical visits for a large proportion of the cohort, provides one of the best opportunities to study joint effects of radiation and other breast cancer risk factors.

Multiple published studies have addressed radiation risk of female breast cancer incidence and mortality in the LSS (*2, 3, 17–19*), but few have focused on breast cancer risk in relationship to reproductive factors (*15, 20,*

21). The most extensive is a case-control study by Land *et al*. (*20*), in which evidence of multiplicative interaction was found between radiation and age at first full-term pregnancy, number of births and cumulative lactation history among females with breast cancer diagnosed through 1985. Goodman *et al*. (*15*) also examined breast cancer risk in relationship to hormonal and reproductive factors but the analysis, restricted to females who responded to a 1980 mail survey, was unable to distinguish between multiplicative or additive joint effects of radiation and various reproductive variables. McDougall *et al*. (*21*) found no variation in radiation risk for breast cancer (diagnosed through 2002) with reproductive status at the time of the bombing (i.e., before menarche, between menarche and first birth and after first birth).

Male breast cancer is rare and, consequently, much less is known about its etiology and radiation effect (*22, 23*) than female breast cancer. Several published studies suggested increased risk with exposure to ionizing radiation (*24, 25*) with the most convincing evidence coming from the LSS (*25*) with an estimated ERR per Gy of 8 based on seven male breast cancers with dose estimates.

The current study is part of a new series on solid cancer incidence reports in the LSS (*26, 27*). The goal of the study is to evaluate radiation effects on breast cancer in females and males through 2009, adding 11 years of follow-up to the previously reported work, using revised dose estimates (DS02R1) (*26*), and incorporating data on reproductive and lifestyle factors from multiple mail surveys in females. The focus of the analyses in females is on effect modification pattern of radiation risk by age and reproductive history.

MATERIALS AND METHODS

Study Population and Case Ascertainment

Study methods have been described in detail elsewhere (*27*). Briefly, the LSS consists of 120,321 subjects, of whom 70,146 (58%) are female. As shown in the literature (*2, 3, 27*), residents of Hiroshima and Nagasaki who were not in either city at the time of the bombings (NIC residents, 22% of the cohort) were included in the analyses to improve estimates of baseline rates and temporal patterns. Analyses were based on 62,354 females and 42,910 males with dose estimates who were alive and did not have a history of cancer as of 1958. Vital status was ascertained through the national family registry system. Incidence follow-up started in 1958 when the Hiroshima and Nagasaki cancer registries became operational and ended on December 31, 2009. Ascertainment of incident cancer cases was conducted primarily via linkage to these registries supplemented by information from the Adult Health Study (AHS), a subset of the LSS that receives biennial health examinations, and surgical and autopsy programs at the Radiation Effect Research Foundation (RERF) active between 1948 and 1988.

Analyses included only first primary breast cancers (ICD-10: C50) diagnosed in the cancer registry catchment areas between 1958 and 2009. Two female breast cancers diagnosed during autopsy were not regarded as cases, as shown by Grant *et al*. (*27*).

Radiation Doses

Dosimetry System 2002 Revision 1 (DS02R1) (*26, 28*) was used to estimate individual organ doses received by those exposed to radiation from the bombings. Estimated doses were adjusted to account for implausibly large estimates (shielded kerma >4 Gy) and random errors in dose assignments. Analyses use weighted absorbed breast doses calculated using a neutron weighting factor of 10 (*19*).

Reproductive Factors and Selected Lifestyle Data

Self-reported information on lifestyle factors and reproductive history was collected in mail surveys conducted in 1969, 1978 and 1991 and AHS clinic-based questionnaires administered in 1963, 1965 and 1968. We considered data on reproductive history, smoking habits and body mass index (BMI) because these have been associated with risk of sporadic or radiation-related breast cancer in different populations (*11, 29–32*). The available reproductive information included age at menarche, parity, number of full-term pregnancies, age at first full-term pregnancy, and menopause status, type and age (as of last answered questionnaire). Overall, the proportion of females with available questionnaire information varied between 47% for age at menarche to 62% for smoking history (Supplementary Table S1; http://dx.doi.org/10.1667/RR15015.1.S1). The mean age of females as of the last questionnaire was 61 years ranging between 19 to 105 years; 75% of females were older than 50 years and 87% were older than 45 years. Because all females surviving beyond a certain age experience natural menopause, we imputed menopausal status and age at menopause if such information was unavailable or outdated. Both variables were treated in the analysis as time-dependent covariates. See Supplementary Materials for details. A missing-value indicator was used in the background rate models for females whose age at menarche was unknown, while menarche age 15 (mean age for females with known information) was imputed in the analyses of radiation effect modification. We defined the overall number of reproductive years as the difference in imputed ages at menopause and menarche and used it as a surrogate measure of ovarian function in analyses of radiation effect modification (see below). In addition, we estimated the number of reproductive years after radiation exposure as the difference in imputed age at menopause and the maximum of age at exposure and age at menarche.

Data Organization

The analyses were based on highly stratified tables of person-time and number of breast cancer cases among females and males by city, age at exposure, attained age, time period, NIC status, DS02R1 weighted absorbed breast dose and a high-dose indicator. Further time-dependent stratification in females was made for reproductive variables, smoking and BMI, as described in the Supplementary Materials (http://dx.doi.org/10.1667/RR15015.1.S1).

Person-years (PY) of observation were computed from January 1, 1958 until the earliest date of first primary cancer diagnosis (including hematopoietic cancers and cancers diagnosed outside of the catchment area, but excluding *in situ* cancers and intramucosal colorectal carcinomas), date of death, 110th birthday or December 31, 2009. Since cancers that were diagnosed outside of the catchment areas were not ascertainable, PYs were adjusted for migration into and out of the catchment areas by applying sex-, age- and time-dependent residence probabilities estimated from the AHS clinical contact data, as in (*27*).

Statistical Analyses

We used Poisson regression to model breast cancer incidence rates as functions of radiation dose (d), city (c), attained age (a), age at exposure (e), birth year (b) and other factors (f) such as age

at menarche, menopause, etc. In describing background rates, we distinguished between in-city and NIC residents (n) in such a way that radiation effects were quantified relative to in-city cohort members with 0 dose (*33*). Radiation effects were modeled using both the ERR and EAR models that describe the observed rates as:

$$\lambda_0(c,a,b,n,f)[1 + ERR(d,a,e,f)]$$

$$\lambda_0(c,a,b,n,f)[1 + EAR(d,a,e,f)]$$

where λ_0 is the background rate for unexposed (0 dose) individuals, $ERR(d,a,e,f)$ describes change in rates due to radiation relative to the background rates allowing for modification of the radiation effect by attained age, age at exposure and other factors, while the $EAR(d,a,e,f)$ describes the difference in rates for those exposed to dose d and those with zero dose.

In females, logarithms of background cancer rates were modeled as a quadratic spline in log-attained age with knots at 50 and 70 years to allow for less rapid increase in rates around the time of menopause, while birth year, age at menarche, number of full-term pregnancies, age at first pregnancy and time to and from menopause were modeled as log-linear trends. Indicator variables for nulliparity and post-menopausal high BMI ($\geq$25 vs. $<$25 kg/m^2) were also included in the final background model. In males, logarithms of cancer rates were modeled as a linear trend in log-attained age. Factors included in the background model were based on likelihood ratio tests (LRT) and/or prior epidemiological evidence about established risk factors for sporadic breast cancer. For more details see Supplementary Materials (http://dx.doi.org/10.1667/RR15015.1.S1).

Models of the form, $\rho(d)\varepsilon(a,e,f)$, were used to characterize the ERR and EAR. In these models, $\rho(d)$ describes shape of the dose response, while $\varepsilon(a,e,f)$ describes radiation effect modification. We considered several models for dose response shape [$\rho(d)$] including:

linear: βd;

linear-quadratic: $\beta d + \gamma d^2$;

and categorical: $\sum_i \theta_i I(D_i \leq d \leq D_{i+1}$.

The primary test for nonlinearity involved testing the hypothesis that $\gamma = 0$ in the linear-quadratic model on the full dose range and on restricted dose ranges. The latter tests were performed using methods described by Grant *et al*. (*27*). In plots showing categorical dose-response estimates, the fitted functions, plotting positions and confidence bounds were smoothed using running weighted-average smoothers, as shown in ref. (*27*).

Radiation effect modification was generally described using multiplicative log-linear models in which the modifying variables were centered and scaled so dose-response parameters correspond to the risk at attained age 70 after exposure at age 30 (unless specified otherwise) and effect-modification parameters describe the change in risks for a given change in the factor of interest (such as powers of age or changes in the risk per decade increase in age at exposure). Some analyses examined nonlinear modifying functions. These typically involved quadratic functions, although multi-knot splines were also considered, particularly for age at exposure for which we considered a spline with a knot at the age at menarche. All demographic, reproductive and lifestyle factors were evaluated for radiation effect modification.

Estimated parameters, LRTs and likelihood-based 95% confidence intervals (CI) were computed with the AMFIT module of the Epicure software (Risk Sciences International Inc., Ottawa, Canada) (*34*).

Ethical Considerations

This study was approved by the RERF Human Investigation Committee via approval of Research Protocols 1-75 (Study of Life-span of A-bomb survivors, Hiroshima and Nagasaki) and 18-61 (Tumor registry study in Hiroshima and Nagasaki). The Hiroshima and Nagasaki Prefectures approved the linkages between LSS cohort and data from the Cancer Registries, while the Hiroshima and Nagasaki Medical Associations approved the linkages with their tumor tissue registries.

RESULTS

Characteristics of Breast Cancer Cases and Crude Incidence Rates

Between 1958 and 2009, we identified 1,470 incident breast cancers among 62,534 females and 10 among 42,910 males (Table 1). Female cases included 397 cases diagnosed since the previously reported study, 75% of which occurred among those exposed before age 20. Altogether, 53% of the female cases were less than 20 years of age at the time of exposure. Nearly 95% of cases had histological confirmation while only 1.6% were based solely on death certificates. The overall rate of female breast cancer was 7.59 per 10^4 PY. Crude rates were higher in Hiroshima than Nagasaki ($P = 0.018$, Table 1), increased with attained age ($P < 0.001$) and decreased with age at exposure ($P < 0.001$). Rates also increased with increasing dose ($P < 0.001$) and were slightly higher for females in the NIC group than those exposed to $<$0.005 Gy.

In males, the overall breast cancer rate was 0.09 per 10^4 PY (Table 1). There were two cases of male breast cancer among NIC survivors and eight among proximal survivors; the crude rates of male breast cancer were comparable in the Hiroshima and Nagasaki survivors ($P = 0.960$, Table 1), and increased with dose ($P = 0.013$); the rates in males also tended to increase with attained age ($P = 0.081$) and age at exposure ($P = 0.128$).

Reproductive Factors and Selected Lifestyle Data

Availability of reproductive and lifestyle factors in females and descriptive statistics for these variables are presented in Supplementary Table S1 (http://dx.doi.org/10.1667/RR15015.1.S1). The proportion of females with information was consistently lower among those born before 1910 due to the age of these survivors in 1968 at the time of the first survey. The mean age at menarche, number of full-term pregnancies, proportion of nulliparous and ever-smoking females decreased with increasing year of birth, while age at first full-term pregnancy and the proportion of females with artificial menopause increased. There was little variability in mean age at menopause and BMI with birth years.

Background Rates

As in previously published analyses (*3*), background rates in females were described in terms of attained age, city, year of birth and NIC status adjusted for radiation dose. We also considered the effects of reproductive factors, BMI and smoking (Table 2). For a given attained age, background rates significantly increased with increasing year of birth. The estimated increase was

TABLE 1
Number of People, Incident Breast Cancer Cases, Person-Years of Follow-up and Crude Incidence Rates by Selected Characteristics: LSS Solid Cancer Incidence Cohort, 1958–2009

	No. of people	PY	No. of cases	Rate per 10^4 PY	P^a
Females					
Total	62,534	1,937,390	1,470	7.59	
City					0.018
Hiroshima	43,903	1,385,565	1,092	7.88	
Nagasaki	18,631	551,744	378	6.85	
Age at exposure (years)					<0.001
0–19	24,199	901,471	778	8.63	
20–39	21,564	749,915	553	7.37	
40–	16,771	286,004	139	4.86	
Attained age (years)					<0.001
<40	32,865	353,318	64	1.81	
40–	10,371	298,896	221	7.39	
50–	9,841	385,402	322	8.35	
60–	6,030	413,010	363	8.79	
70–	2,775	313,286	320	10.21	
80–	652	173,478	180	10.38	
DS02R1 weighted absorbed breast dose (Gy)					<0.001
NIC	14,818	574,891	400	6.96	
<0.005	20,575	529,938	320	6.04	
0.005–	16,234	502,414	337	6.71	
0.1–	3,422	105,361	91	8.64	
0.2–	3,711	112,049	118	10.53	
0.5–	2,156	65,480	99	15.12	
1.0–	1,118	33,479	69	20.61	
2.0–	500	13,777	36	26.13	
Males					
Total	42,910	1,142,169	10	0.09	
City					0.960
Hiroshima	29,498	807,695	7	0.09	
Nagasaki	13,412	334,475	3	0.09	
Age at exposure (years)					0.128
0–19	21,588	727,742	4	0.05	
20–39	8,525	238,554	3	0.13	
40–	12,797	175,873	3	0.17	
Attained age (years)					0.081
<60	35,477	709,649	3	0.04	
60–	5,228	238,151	4	0.17	
70–	2,205	194,370	3	0.15	
DS02R1 weighted absorbed breast dose (Gy)					0.013
NIC	10,488	287,797	2	0.07	
<0.005	14,119	367,633	2	0.05	
0.005–	13,244	357,425	2	0.06	
0.2–	2,345	61,812	2	0.32	
0.5–	2,714	67,503	2	0.30	

Note. LSS solid cancer incidence cohort with known doses.
[a] *P* value for heterogeneity or trend.

36% per decade ($P < 0.001$). Variation in background rates with attained age was described using a quadratic spline with knots at ages 50 and 70, i.e., rates strongly increased up to the mid-50s, leveling off around menopause and increasing again thereafter (Supplementary Fig. S1 and Table S2; http://dx.doi.org/10.1667/RR15015.1.S1). The estimated age-specific rates in Nagasaki were 12% lower than in Hiroshima ($P = 0.045$), while there was no evidence that background rates differed for NIC and in-city survivors ($P = 0.681$).

For the same birth cohort and attained age, breast cancer rates significantly decreased with increasing number of full-term pregnancies (–12% per each additional pregnancy, $P < 0.001$), but not with age at first pregnancy ($P = 0.173$) or age at menarche ($P = 0.131$). Age-specific rates in nulliparous females were 27% higher than those in females who had one full-term pregnancy ($P = 0.055$). Menopause had complex effects on breast cancer rates. Among premenopausal females of a given age, rates were 4.9% higher for those who were one year closer to menopause ($P = 0.029$). For post-menopausal females of a given age, rates were 3.6% lower for those who were one year farther from menopause ($P < 0.001$). Being overweight or obese was associated with 70% higher rates of breast cancer among

TABLE 2
Selected Associations with Background Incidence of Breast Cancer: Female LSS Solid Cancer Incidence Cohort with Known Doses, 1958–2009

	% Change (95% CI)[a,b]	*P*
Nagasaki (vs. Hiroshima)	–11 (–22 to 0)	0.045
NIC (vs. in-City)	–3 (–15 to 11)	0.681
Birth cohort (per decade)	36 (29 to 44)	<0.001
Age at menarche (per year)	–4 (–9 to 1)	0.131
Nulliparous (vs. females with one live birth)	27 (–0.5 to 61)	0.055
Number of full-term pregnancies (per pregnancy)	–12 (–17 to –8)	<0.001
Age at first full-term pregnancy (per year)[d]	1.4 (–0.6 to 3.5)	0.173
Time to menopause (per year)[c]	4.9 (0.5 to 9.3)	0.029
Time from menopause (per year)[c]	–3.6 (–5.3 to –1.8)	<0.001
High BMI premenopause (≥25 vs. <25 kg/m²)[d]	–11 (–53 to 53)	0.703
High BMI postmenopause (≥25 vs. <25 kg/m²)	70 (45 to 98)	<0.001
Current smoker (vs. never smoker)[d]	–8 (–25 to 13)	0.450
Past smoker (vs. never smoker)[d]	–1.7 (–29 to 32)	0.915

Note. Female LSS solid cancer incidence cohort with known doses; 95% confidence interval.

[a] Estimates are adjusted for city, year of birth, NIC, attained age, age at menarche, parity, number of full-term pregnancies, high BMI postmenopause, and time to and from menopause and simple linear dose effect with attained age modification and high dose adjustment.

[b] Negative values are percentage decreases and positive values are percentage increases.

[c] These effects are for females of the same attained age who are one year closer to menopause (time to) or one year farther from menopause (time from).

[d] These factors were not kept in the final background model.

postmenopausal females ($P < 0.001$), with no apparent effect among premenopausal females ($P = 0.703$). Among females with known smoking history, 82% were never smokers (Supplementary Table S1; http://dx.doi.org/10.1667/RR15015.1.S1) and neither current ($P = 0.450$) nor past smoking ($P = 0.915$) was associated with increased rates of breast cancer. The percentage changes in background rates (Table 2) were based on our preferred ERR model described below and in Supplementary Table S3.

Due to the small number of male breast cancer cases, characterization of background rates was simpler than in females and included only the effect of attained age modeled as a log-linear trend ($P = 0.013$).

Radiation Effects

ERR models. A linear dose-response model, with background rates modeled as described above and no effect modification, provided strong evidence of a radiation dose response in females ($P < 0.001$). Allowing for effect modification by age at exposure and attained age, the estimated linear ERR at attained age 70 after exposure at age 30 was 1.12 per Gy (95% CI: 0.73 to 1.59, Supplementary Table S4; http://dx.doi.org/10.1667/RR15015.1.S1). This estimate is similar to that obtained when fitting the model used in the previously reported analysis (*3*) to the current data (1.06; 95% CI: 0.69 to 1.51, Supplementary Table S5).

There were no significant departures from linearity over the full dose range ($P = 0.096$) or when range was limited to 0–2 Gy ($P = 0.152$, Supplementary Table S6; http://dx.doi.org/10.1667/RR15015.1.S1). Figure 1 shows the fitted dose-response plots over the full dose range (Fig. 1A) and under 1.25 Gy (Fig. 1B). These were based on a preferred model that included effect modification by attained age, age at menarche and age at exposure (described below and in Supplementary Table S3). The plotted dose-response functions are for a 70-year-old female who was exposed and experienced menarche at age 15. In this case the estimated ERR at 1 Gy was 1.40 (95% CI: 0.85 to 2.15). For comparison, the ERR at 1 Gy for a 70-year-old female exposed at age 30 who experienced menarche at age 15 was 1.04 (95% CI: 0.61 to 1.51). The linear ERR per Gy estimates were stable for successively lower dose ranges down to 0.250 Gy (Supplementary Table S6).

The male dose response was statistically significant ($P = 0.018$) with an estimated linear ERR per Gy of 5.7 (95% CI: 0.3 to 30.8).

Effect modification of ERR. As in previously reported analyses (*2, 3*), the ERR in females decreased with attained age ($P = 0.001$), but, unlike earlier analyses in which there was strong evidence for modifying age-at-exposure effects in models that did not allow for effect modification by attained age, there was only a suggestion ($P = 0.07$) of such an effect in the current data. Allowing for independent modifying effects of attained age and age at exposure, the ERR decreased in proportion to age to the power of –1.5 (95% CI: –2.6 to –0.4, $P = 0.007$, Supplementary Table S4; http://dx.doi.org/10.1667/RR15015.1.S1), while the estimated nonsignificant decrease in the ERR was –5% per decade increase in age at exposure (95% CI: –23% to 15%, $P = 0.58$). There was no evidence that radiation effect differed by city ($P = 0.21$) or smoking status ($P > 0.5$).

Examining effect modification by reproductive variables and BMI, while allowing the ERR to vary by attained age, we found a strong, independent modifying effect of age at menarche ($P = 0.007$), but not of other factors (Supplementary Table S7; http://dx.doi.org/10.1667/RR15015.1.S1). These included menopausal status ($P = 0.630$), age at menopause ($P = 0.145$), time to menopause ($P = 0.583$) and time from menopause ($P = 0.578$), overall number of reproductive years ($P = 0.099$) and number of reproductive years after radiation exposure ($P = 0.118$). The estimated decrease in the ERR based on a preferred model was –24% per year increase in age at menarche (95% CI: –37% to –8%). The variation in the ERR with attained age for different ages at menarche and exposure is plotted in Fig. 2. This figure shows that the ERR decreases with increasing attained age for any age at exposure and menarche and that,

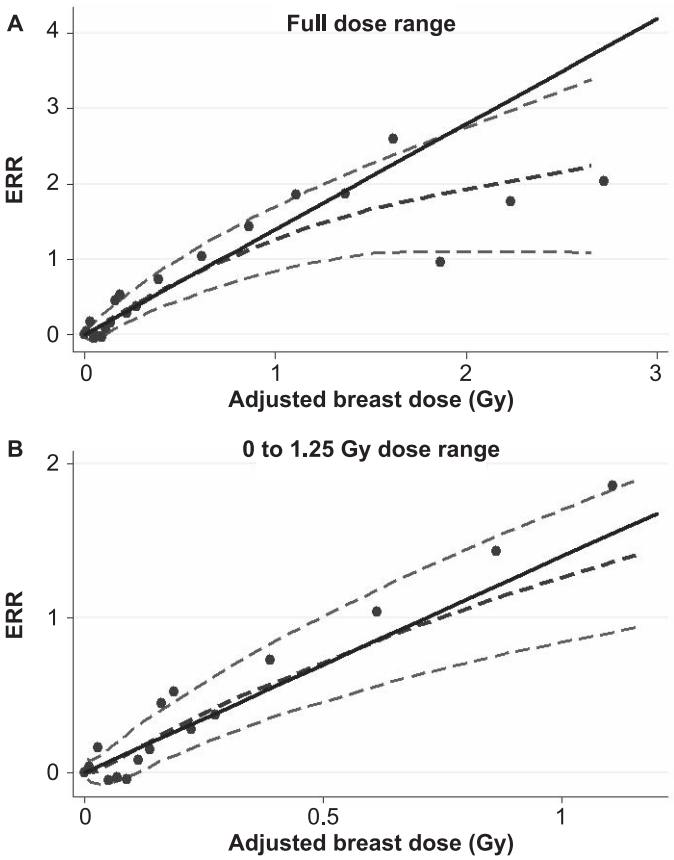

FIG. 1. Female breast cancer excess relative risk (ERR) in relation to weighted absorbed DS02R1 breast dose. These estimates are for 70-year-old females exposed at age 15 with an age at menarche of 15. The linear ERR is 1.40 per Gy (95% CI: 0.85 to 2.15). Panel A: Fitted linear ERR dose-response function (solid black line), the ERR estimates for 22 dose categories (black points) and a nonparametric smoothed estimate with pointwise 95% confidence intervals (dashed curves) over the entire dose range. Panel B: Same data as in panel A, in the low dose range (0–1.25 Gy).

for a given attained age and age at exposure, the ERR is higher for females with earlier menarche.

The magnitude of decrease in the ERR with increasing age at menarche was not significantly different ($P = 0.136$) whether menarche was experienced before (–31%; 95% CI: –43% to –13%) or after exposure (–14%; 95% CI: –33% to 12%). However, there was a suggestion that, for the same attained age and age at menarche, the ERR followed a non-monotonic function in age at exposure described by a log-linear spline with a knot at age of menarche ($P = 0.043$ relative to the model with a log-linear age-at-exposure trend). The addition of a second knot at age of first full-term pregnancy, to allow for different trends in ERR with age at exposure before and after first pregnancy, did not result in further improvement in fit ($P = 0.401$ relative to a model with a single knot at age at menarche). For a given attained age and age at menarche, the preferred single-knot age-at-exposure model indicates that radiation risks increase as age at exposure approaches menarche and slowly decrease after menarche (Fig. 3). The evidence for an increase with age at exposure before menarche was somewhat stronger ($P = 0.06$) than for a decrease after menarche ($P = 0.20$). Together, Figs. 2 and 3 demonstrate that the highest ERRs are estimated for young females with early menarche and exposure around menarche age.

EAR models. An EAR model with log-linear-quadratic effect modification in log-attained age along with age-at-menarche and age-at-exposure spline (as in the ERR model) provided a fit that was slightly worse than the ERR model (deviance of 15,593.214 and 15,596.445, respectively). Under this model, for any age at exposure and menarche, the fitted EARs increase for ages up to approximately 70 years and then decrease slightly for later ages ($P < 0.001$), while, at any given attained age and age at exposure, the EARs decrease with increasing age at menarche (–29% per year increase in age at menarche, 95% CI: –40% to –15%, $P < 0.001$) as in the ERR model. The plots in Fig. 4 display the EAR at 1 Gy as a function of attained age for various combinations of ages at menarche and exposure.

As with the ERR, the EAR exhibited non-monotonic variation with age at exposure before and after menarche ($P = 0.015$ for a single-knot spline relative to model with a log-linear age-at-exposure trend), while the addition of a second knot at age of first full-term pregnancy described data somewhat worse than a model with a single knot at age at menarche ($P = 0.064$). Excess rates in the single-knot model declined significantly ($P < 0.001$) with age at exposure for exposures after menarche. Even though the pre-menarche age-at-exposure effect differed significantly from the post-menarche effect ($P = 0.015$), there was no indication of statistically significant variation in the EAR with age at exposure when exposure occurred before menarche ($P = 0.340$). We fitted two single-knot splines, one with unconstrained trend in age at exposure before menarche (as in the ERR model) and another with the trend constrained to be constant. Figure 5 shows the variation in EAR at 1 Gy with age at exposure based on a spline with no age-at-exposure trend before menarche for selected combinations of attained age and age at menarche. Together, Figs. 4 and 5 show that the highest excess rates were estimated for females of approximately 60–70 years of age who experience early menarche and were exposed before or around that time.

The parameter estimates from the preferred EAR model are summarized in Supplementary Table S8 (http://dx.doi.org/10.1667/RR15015.1.S1).

DISCUSSION

With 11 additional years of follow-up, the number of female breast cancer cases increased by 397 (or 37%) since the previously reported analysis (*3*). Most new cases were among females exposed before age 20, increasing statistical

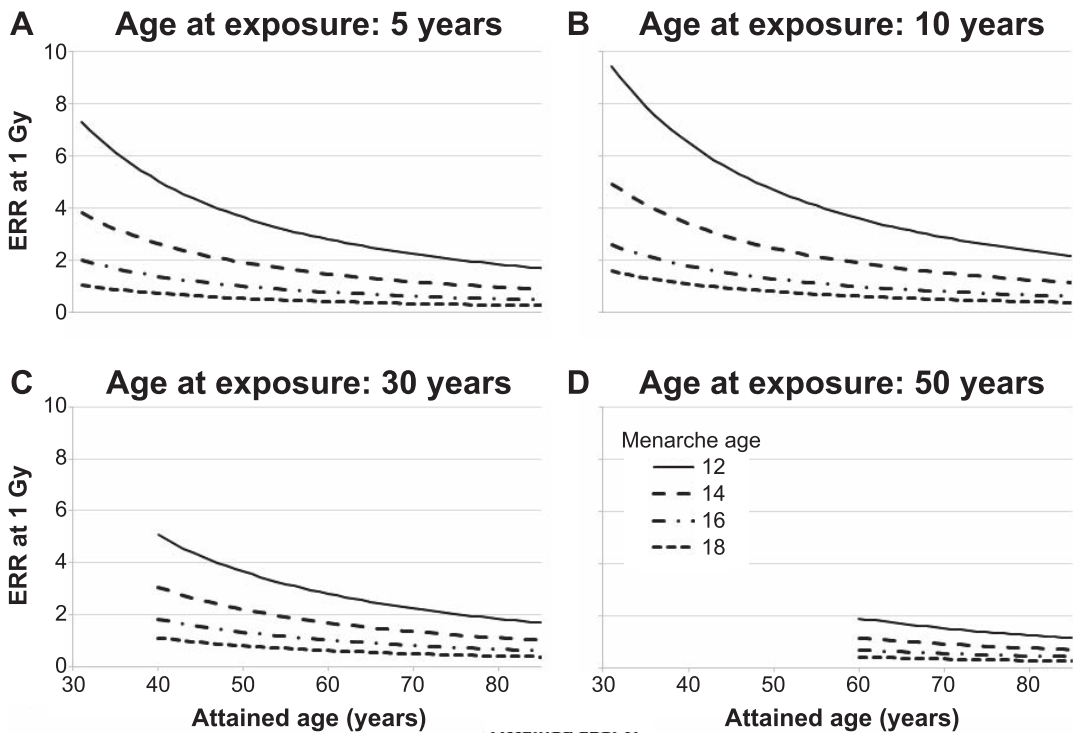

FIG. 2. Estimated ERR at 1 Gy for female breast cancer incidence in the Life Span Study by attained age for selected ages at exposure (5, 10, 30 and 50 years, for panels A–D, respectively) and menarche ages of 12 (solid curves), 14 (dashed curves), 16 (dash-dotted curves) and 18 (dotted curves) years. Estimates are from a linear dose-response model with effect modification by attained age, age at menarche and age at exposure.

power to address long-term effects of radiation exposure at young ages. We continue to find a strong breast cancer dose response consistent with linearity. The ERR per Gy remained stable as analyses were limited to successively lower dose ranges down to 0.250 Gy. The ERR was significantly modified by attained age, with the estimated ERR per Gy of 1.12 for a 70-year-old female after exposure at age 30 without allowance for effect modification by age-at-menarche, which was similar to the previously reported estimate (*3*). In addition, age at menarche had an independent modifying effect on the ERR (24% decrease in the ERR per year increase in age at menarche); the ERR

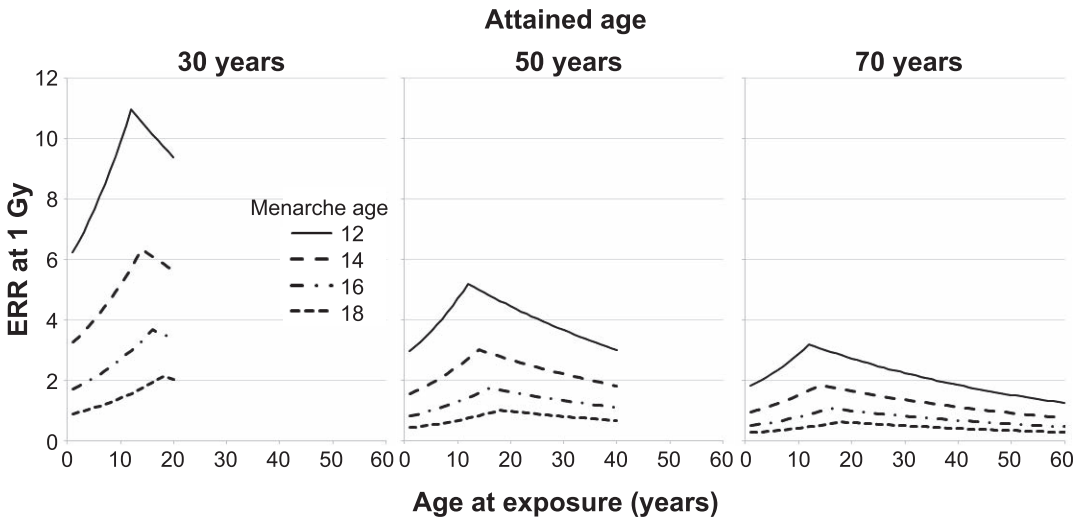

FIG. 3. Estimated ERR at 1 Gy for female breast cancer incidence in the Life Span Study by age at exposure for selected attained ages (30, 50 and 70 years) and menarche ages of 12 (solid curves), 14 (dashed curves), 16 (dash-dotted curves) and 18 (dotted curves) years. Estimates are from a linear dose-response model with effect modification by attained age, age at menarche and age at exposure.

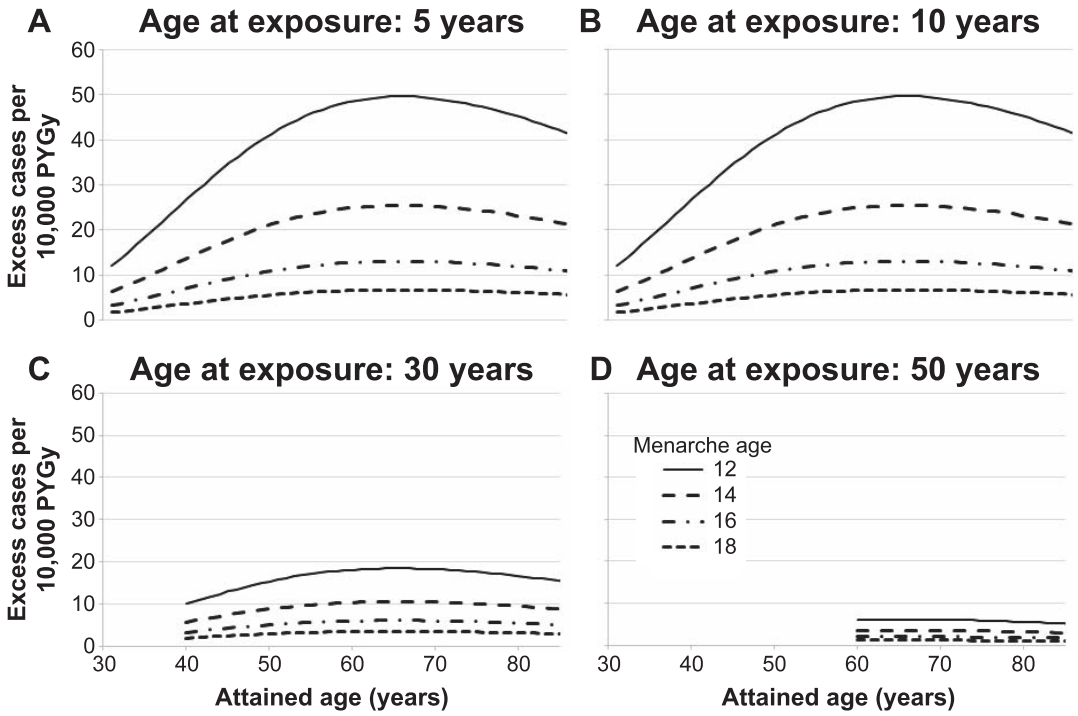

FIG. 4. Estimated excess absolute rate (EAR) per 10,000 PY Gy for female breast cancer incidence in the Life Span Study by attained age for selected ages at exposure (5, 10, 30 and 50 years, panels A–D, respectively) and menarche ages of 12 (solid curves), 14 (dashed curves), 16 (dash-dotted curves) and 18 (dotted curves) years. Estimates are from a linear dose-response model with effect modification by attained age, age at menarche and age at exposure.

at 1 Gy for a female at attained age 70, with age at menarche of 15 and exposure at age 30, was 1.04. In absolute risk, the EAR increased with increasing attained age up to age 70 and then declined slightly, reflecting the age pattern of baseline rates in females. Age at menarche was also a significant modifier of the EAR (29% decrease in the EAR per year increase in age at menarche). Additional analyses suggested a non-monotonic pattern of the ERR and EAR by age at exposure before compared to after menarche (see further discussion below).

For males, the number of breast cancers remained low, increasing only by one since the previously reported

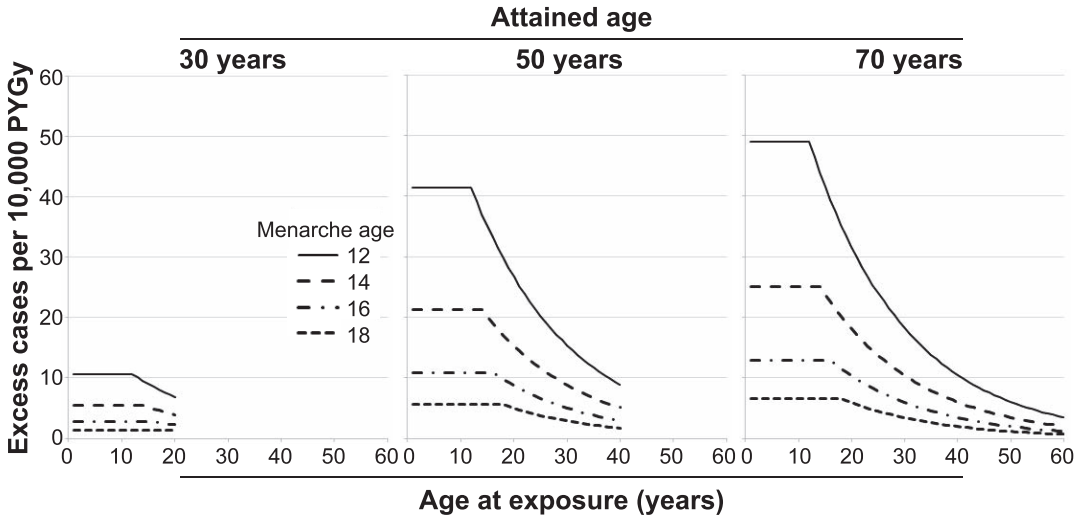

FIG. 5. Estimated EAR per 10,000 PY Gy for female breast cancer incidence in the Life Span Study by age at exposure for selected attained ages (30, 50 and 70 years) and menarche ages of 12 (solid curves), 14 (dashed curves), 16 (dash-dotted curves) and 18 (dotted curves) years. Estimates are from a linear dose-response model with effect modification by attained age, age at menarche and age at exposure.

analysis (*25*), and the data continue to suggest a striking radiation effect with an estimated ERR per Gy of 5.7.

Attained Age and Age-at-Exposure Effects on Radiation Risks

The estimated decrease in the ERR with attained age in the current analysis is somewhat less rapid (proportional to one over age to the power 1.5) than in previous analysis (proportional to one over age to the power 2.3) (*3*). As indicated elsewhere (*3*), the increase in the EAR with attained age was approximately proportional to attained age to the power 1.6 with some flattening after approximately age 70.

Our understanding of the relative importance of attained-age and age-at-exposure effects on the ERR and EAR for female breast cancer has evolved over the years (*3, 18, 35*). In early LSS data, the ERR decreased significantly with increasing age at exposure and attained age when these were analyzed separately, but neither remained significant when both were included simultaneously due to their strong correlation (*2, 18*). Previously published analyses have focused on the potential for age at exposure to modify the effect of radiation on breast cancer. However, as follow-up increased, the correlation between attained age and age at exposure in the LSS decreased markedly, making possible an examination of age at exposure and attained age as separate effect modifiers. Over time, the evidence for and estimated magnitude of a simple trend in the ERR with age at exposure has lessened, especially when the ERR was allowed to vary with attained age (*3*). In the current analysis, there was only weak evidence of a significant trend in the ERR per Gy with age at exposure ($P = 0.07$) without allowance for attained-age effect modification. By contrast, after allowing for attained-age effect, the EAR decreased by 37% per decade increase in age at exposure.

Based on knowledge of human breast tissue development and differentiation (*36*) and animal experiments (*36*), it has been proposed that exposure to radiation may be particularly carcinogenic when it occurs during sensitive periods in breast development, such as *in utero*, puberty and pregnancy, which are characterized by rapid proliferation of undifferentiated cells. Specifically, experimental studies suggest that fetal mammary cells possess greater self-renewal capacity and more robust production of progenitors than adult cells, even though the fetal mammary gland is morphologically immature (*37*). During puberty, under rising levels of estrogen, the mammary gland undergoes dramatic changes and develops into a highly branched epithelial network mediated by rapid stem cell proliferation of the terminal end buds (*38*). Another major expansion of breast epithelium occurs during pregnancy and is accompanied by terminal differentiation of mammary lobules (*39*). The detailed mechanism by which radiation exposure during sensitive periods might stimulate breast cancer development is unknown; however changes in tissue composition and stem cell regulation after exposure are gaining more support.

There are several reported epidemiological studies in which breast cancer risk has been evaluated after radiation exposure during these periods, with inconclusive results (*11, 13, 14, 21*). In one study of 1,764 females with pulmonary tuberculosis, who were exposed to multiple chest fluoroscopies to monitor lung collapse therapy, higher risks with irradiation were observed at time of menarche or first pregnancy (*13*). A study of breast cancer, after radiotherapy for Hodgkin disease (HD), reported significantly increased risks in patients treated within six months of menarche that increased with proximity of radiation therapy to menarche but not to first full-term pregnancy (*14*). Another study of childhood cancer survivors, not limited to HD and exposed to chest radiotherapy, found lower but substantially elevated radiation risk of breast cancer (*40*). However, no variation was found in the ERR in relationship to stage of reproductive development (pre-menarche, between menarche and first birth and after first birth) in a study of females with spine deformities who had undergone multiple diagnostic X rays (*11*) and LSS cohort subjects with known reproductive histories (*21*) once these were controlled in the background.

Our study extends available human data concerning sensitivity of breast tissue to radiation exposure during puberty (*13, 14*). The current analyses benefited from the increased number of cases who were exposed at that time, and used a flexible analytic approach that allowed for separate age-at-exposure trends before and after menarche or first full-term pregnancy. We found that, for a given age at menarche, exposure around the time of menarche results in the largest radiation effects both on the ERR and EAR scale with different trends for exposures before and after menarche. For exposures prior to menarche, radiation effect increases (ERR) or remains stable (EAR) as the exposure age approaches menarche, while for exposures after menarche, radiation effects (ERR and EAR) decrease as exposure age increases. In contrast, we found no evidence that age-at-exposure effects on ERR and EAR differ before and after first full-term pregnancy. Taken together, our findings support a hypothesis of increased breast tissue sensitivity to radiation during puberty but not first pregnancy.

Effects of Reproductive and other Factors on Radiation Risks

For reproductive factors, other than age at menarche, the current analysis found no radiation effect modification nor was it possible to distinguish between additive and multiplicative joint effects of radiation and these factors. However, we found, for the first time, significant evidence that age at menarche acts as a modifier of breast cancer radiation effects with higher ERR and EAR for those with earlier than later menarche. In the published case-control

study of breast cancer by Land *et al*. (*20*), age at menarche was unassociated with breast cancer risk after controlling for radiation dose, and a modifying effect of age at menarche was not considered. This study, conducted in the mid-1980s, included fewer breast cancer cases who were children or adolescents at the time of the bombs than the current study (41 vs. 523 cases, respectively). Land *et al*. (20) did find the joint effect of radiation and early age at first full-term pregnancy, number of deliveries and cumulative lactation period being consistent with a multiplicative model, that is, the ERR per Gy did not vary significantly with levels of reproductive factors. Cumulative lactation history obtained by Land *et al*. via personal interviews was unavailable from the mail surveys used in the current study.

Because age at menarche was unknown for many females in the earlier birth cohorts, we restricted the analyses to females with known age at menarche or those born after 1910 and found little impact on the results. Dose and age at menarche are uncorrelated in the full LSS cohort or within birth cohorts, thus it seems unlikely that this effect results from residual confounding by dose.

To our knowledge, the modifying age-at-menarche effect on radiation risks has not been reported elsewhere. Other studies may have been underpowered to detect it due to limited sample size, range of doses and/or ages at menarche. In the LSS, there is a wide, birth-cohort-dependent variation in age at menarche (i.e., younger age in more recent birth cohorts) with a substantial fraction of females experiencing menarche at >14 years (80%). The observed age-at-menarche effects suggest that factors related to timing of menarche may affect radiation risks throughout life. These could include genetic and environmental influences, not limited to the window of breast tissue exposure to estrogens (*41, 42*). However, in the absence of similar findings in other studies, generalization of this effect beyond the LSS should be done with caution.

In the current study, the radiation risks did not vary significantly by menopause-related variables including age at menopause and number of reproductive years, a surrogate measure of ovarian function and breast tissue exposure to estrogens. By contrast, several published studies of childhood cancer survivors exposed to high radiation doses to the chest showed higher breast cancer risks with late menopause ($\geq$40 years) compared to early menopause ($<$40 years) and $\geq$10 years of ovarian function after radiotherapy compared to $<$10 years (*14, 43*). Comparison of radiation risks with childhood cancer survivors is complicated by the fact that some patients might experience premature ovarian failure due to pelvic irradiation (*40*) or alkylating agents (HD patients) and are exposed around menarche (*7, 43, 44*); in addition, attained age of childhood cancer survivors (*14, 23*) is substantially lower than the current LSS cohort.

The strengths of our study include a large number of histologically confirmed breast cancer cases in a large, well-defined cohort with long follow-up, and individual radiation dose estimates for virtually all cohort members. Breast cancer cases in the LSS cohort were ascertained by linkage with the population-based tumor registries to which cases are reported, from many hospitals and other sources in Hiroshima and Nagasaki, minimizing potential for under-ascertainment (*45*). In an earlier published incidence study, Tokunaga *et al*. concluded that the possibility of under-ascertainment and its correlation with radiation dose seemed unlikely (*46*). In our study, individual reproductive history data were available for 47–60% of the female cohort. To maximize statistical power and avoid potential biases, we included all females in the analyses regardless of whether they had reproductive data, and they were treated as having unknown reproductive history until it became known for the first time. The rationale is that, except for BMI, background breast cancer rates did not differ for females with known and unknown status while the associations among females with known status were consistent with those reported in studies of unexposed populations in Japan (*30, 31*) and elsewhere (*29*). There was no evidence that radiation risk estimates differed meaningfully between females with known and unknown reproductive history (Supplementary Table S9; http://dx.doi.org/10.1667/RR15015.1.S1). Therefore, while it reduces our ability to detect modification of radiation risks, we do not believe that having incomplete data resulted in biased risk estimates. Reproductive history was self-reported, although such information is typically reported reliably (*47, 48*) and recall bias is unlikely. Another possible limitation is lack of data on expression of estrogen (ER), progesterone (PR) and human epidermal growth factor receptors (HER2) that define several biologically distinct subtypes of breast cancer (*49–51*). For Western and Japanese populations, associations with reproductive factors vary according to breast cancer subtypes (*50, 51*) but for radiation exposure this is unclear. If there is subtype-specific variation in radiation risk, combining all cancer subtypes might result in under-/overestimation of radiation effects or affect effect modification patterns by age or birth cohort. However, it should be noted that ER-positive tumors account for $\geq$70% of all breast cancers in recent years in unexposed populations (*50–52*). There is an ongoing effort at RERF to assess tumor receptor status in available tissue blocks of breast cancer cases included in the current study and thus, to address subtype-specific associations with radiation dose in the future.

CONCLUSION

The study of the LSS cohort of atomic bomb survivors, spanning more than 64 years after exposure, continues to show a strong dose response for both female and male breast cancer. Among females, there is a marked reduction in ERR and increase in EAR with attained age. The modifying effects of age at menarche and independent non-

monotonic age at exposure on radiation risks suggest increased breast tissue sensitivity in females during puberty.

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