

Research Article

Timing of Menarche and First Birth in Relation to Risk of Breast Cancer in A-Bomb Survivors

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Abstract

Background: The length of the interval between age at menarche and age at first birth is positively associated with breast cancer risk. We examined the risk of breast cancer in atomic bomb survivors to investigate whether women exposed to radiation between menarche and first birth had a higher risk of radiogenic breast cancer than women exposed at the same age but outside this interval.

Methods: Women ($n = 30,113$) were classified into three reproductive status at the time of the bombings (ATB) categories (premenarche, between menarche and first birth, or after first birth). Poisson regression was used to test the primary hypothesis.

Results: When the background rate of breast cancer was taken to depend on city, age ATB, and attained age only, the radiation-related excess relative risk (ERR) varied significantly among the three categories ($P = 0.049$). However, after controlling for significant heterogeneity in the baseline risk of breast cancer between reproductive status ATB groups ($P < 0.001$), no significant heterogeneity ($P = 0.88$) was observed in the ERR, with an ERR per Gy of 1.36 [95% confidence interval (CI), 0.54-2.75] for women exposed between menarche and first birth ATB, and 1.07 (95% CI, 0.22-3.62) and 1.53 (95% CI, 0.63-2.90) for those exposed premenarche or after first birth, respectively.

Conclusions: The radiation-associated risk of breast cancer does not vary significantly by reproductive status ATB.

Impact: It is possible that radiation exerts similar carcinogenic effects on the breast regardless of its stage of differentiation, or that the differences in radiosensitivity are too small to be detected in this cohort. *Cancer Epidemiol Biomarkers Prev*; 19(7); 1746-54. ©2010 AACR.

Background

Early age at menarche and late age at first birth are two well-established breast cancer risk factors (1, 2). Between these two milestones, breast tissue is largely undifferentiated and is thus particularly susceptible to carcinogenic insults (3). It is well established that pregnancy, particularly pregnancy at a young age, reduces the risk of breast cancer (4), and this is primarily because of the differentiation of breast tissue that occurs during pregnancy (5). Circulating hormones released during the menstrual cycle

can have a greater effect on the promotion of breast abnormalities on the nulliparous, relatively undifferentiated breast compared with the parous breast (4). Thus, the longer the interval between menarche and first birth, an interval Russo et al. (5) have described as a "window of high susceptibility," the more a woman's breast tissue is particularly susceptible to carcinogens. A few studies have shown a positive association between the timing of menarche and first birth and breast cancer risk (6, 7). Specifically, Li et al. (6) found a 1.5-fold increase in the risk of breast cancer for women who had an interval of ≥ 16 years between the ages of menarche and first birth in comparison with those who had ≤ 5 years between these ages, and this risk did not vary substantially by menopausal status.

Radiation exposure is another well-established breast cancer risk factor (8, 9). The purpose of this study is to assess how radiation exposure during the interval between menarche and first birth affects breast cancer risk, compared with those exposed to radiation either before experiencing menarche or after their first birth, among female survivors of the atomic bombings of Hiroshima and Nagasaki in 1945. We hypothesize that the radiation-related risk of breast cancer is higher in women exposed to radiation during the period between menarche and

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first birth, compared with women of the same age exposed either before menarche or after their first birth.

Evidence exists from previous studies of atomic bomb survivors that age at exposure to radiation is strongly associated with the subsequent risk of breast cancer, with women exposed before age 20 years having a significantly higher radiation-related excess risk before age 35 years than those exposed later (10). In other irradiated populations, evidence suggests that radiation exposure during a first pregnancy was more strongly associated with an elevation in breast cancer risk than radiation exposure during a later pregnancy (11). However, a recent study of breast cancer risk in a cohort of United States women exposed to diagnostic X-ray radiation showed no significant difference in risk associated with the radiation dose-response between women exposed before breast budding, between budding and menarche, between menarche and first live birth, and after first live birth (12). Previous studies using data from the Life Span Study (LSS) and Adult Health Study (AHS) cohorts of atomic bomb survivors have shown that younger age at exposure is associated with an increased risk of breast cancer, particularly exposure before age 20 years (10). This finding, if true, might be due to the inclusion of many women who were exposed between menarche and first birth in this younger age group. However, the most recent incidence study found that the strength and statistical significance of the estimated effect of age at the time of the bombings (ATB) on radiogenic risk estimates described by Land et al. (10) is highly dependent on the modeling of the background rates (13).

Materials and Methods

This study used data from a subset of participants in the Radiation Effects Research Foundation's (RERF) LSS and AHS cohorts with follow-up through December 31, 2002. The LSS includes 70,146 women with enrollment and follow-up beginning in October 1950. The AHS consists of a subset of the LSS invited to participate in a clinical follow-up study. For the purposes of this study, follow-up begins on January 1, 1958, the start of the comprehensive cancer incidence follow-up through the tumor registries in Hiroshima and Nagasaki. Women with a date of cancer diagnosis or a date of last follow-up before 1958 ($n = 4,073$) were excluded from this analysis. We also excluded women with missing radiation dose ($n = 3,547$), women who were pregnant ATB ($n = 1,459$), and women with missing data on both age at menarche and age at first birth ($n = 36,810$). In addition, cancer cases identified only from death certificate ($n = 71$) or autopsy ($n = 115$) and cancer cases diagnosed outside of either Hiroshima or Nagasaki ($n = 74$) were excluded from this study because person-time at risk could not be accurately determined for these women. This left a total of 30,113 cohort members available for analysis. The total number of person-years contributed by these women was adjusted to reflect the migration of LSS members

from the tumor registry catchment area. Details of the methods used to obtain the migration-adjusted person-years in studies of atomic bomb survivors have been published previously (14). Briefly, the migration adjustment involves reducing the observed person-years by a sex-, age-, time period-, and city-specific probability of an individual's continued residence in the tumor catchment area. The probability of continued residence is based on detailed residence history from surviving AHS cohort members updated periodically by RERF.

Women were assigned to reproductive status categories based on data from LSS mail survey questionnaires and AHS clinical examinations. Data on age at menarche (in years) was available from LSS mail surveys from 1969 and 1978. Information on age at first birth and number of births was available from data obtained from AHS clinical visits in 1963 and LSS mail surveys from 1969, 1978, and 1991. Responses were checked carefully for consistency between questionnaires. The average age at menarche and average age at first birth was used if responses between questionnaires differed by no >2 and 3 years, respectively. Women classified as premenarche had an age at menarche that was greater than their age ATB. Women classified as between menarche and first birth had an age at menarche less than or equal to their age ATB and an age ATB less than their age at first birth. In addition, nulliparous women with age at menarche less than or equal to their age ATB who were less than 50 years old ATB were included as between menarche and a first birth. Women classified as after first birth had an age ATB greater than their age at first birth. We decided not to assign women with missing data to a reproductive status category based solely on age to avoid possible bias due to possible differences between women with complete and missing data.

Dose estimates were obtained from the dosimetry system currently used by RERF (DS02; ref. 15). Individual weighted breast dose estimates are calculated as the sum of the γ -ray dose plus 10 times the neutron dose given in units of Gy. To correct for random error in individual dose estimates, we used uncertainty-adjusted estimates of expected survivor doses calculated by assuming 35% errors in individual DS02 dose estimates (16).

Statistical analysis

The models fit in this study are similar to those used in previous studies of solid cancer incidence in atomic bomb survivors (13). In addition, models were fit to test whether the radiation-related excess risk differed for women in this hypothesized sensitive window compared with women exposed to radiation before experiencing menarche or after experiencing a first birth. Person-years at risk and counts of breast cancer cases were cross-classified by estimated radiation dose to the breast (21 categories each: 0-5, 5-25, 25-50, 50-75, 75-100, 100-125, 125-150, 150-175, 175-200, 200-250, 250-300, 300-500, 500-750, 750-1,000, 1,000-1,250, 1,250-1,500, 1,500-1,750, 1,750-2,000, 2,000-2,500, 2,500-3,000, and >3,000 mGy),

city ($c = 1$ for Hiroshima, 2 for Nagasaki), in city status ($n = 0$ for in city, $n = 1$ for not in city), age at the time of the bombing (15 categories: 0-5, 5-10, ..., 65-70, >70), attained age (17 categories: 5-10, 10-15, ..., 80-85, >85), calendar time (10 categories: 1958-1960, 1961-1965, ..., 1991-1996, and 1997-2002), and reproductive status ATB (three categories: $r = 1$ for premenarche, $r = 2$ for between menarche and first birth, and $r = 3$ for after first birth). The numbers of breast cancers, along with the mean values of the estimated breast dose (d), age at the time of bombing (e), and attained age (a) were calculated for each cell in the data table. Further analyses adjusted for reproductive risk factors were also done, using a second data table with additional cross-classification by age at menarche (≤ 12 , 13-14, 15-16, >16), age at first birth (<20, 20-24, 25-29, ≥ 30), and number of births (0, 1-2, 3-4, >4), from which women with missing data on age at menarche, age at first birth, or number of births were excluded. Results of these additional analyses are not reported here because they did not differ from the analyses adjusting for reproductive status and did not use all of the available data.

Poisson regression analysis was used to estimate the radiation dose-response for breast cancer in this subset of the LSS cohort and to test for dose effect modification by reproductive status. The risk of breast cancer was given by linear excess relative risk (ERR) models of the form

$$\lambda_{d,c,n,a,e,r} = \lambda_0(c, n, a, e, r)[1 + \text{ERR}(d, a, e, r)]$$

in which $\lambda_0(\cdot)$ is the background cancer incidence rate for women with zero dose, and $\text{ERR}(\cdot)$ is the ERR associated with dose d .

The analysis by Preston et al. (13) suggests that the apparent effect of age ATB on radiation-related risk is sensitive to how the baseline risks are modeled. Reproductive status in August 1945 may represent the combined effect of age, birth cohort, and exogenous factors related to wartime deprivation, which might influence the baseline and/or excess risk. Therefore, in our analysis, we examined the possible effects of reproductive status at the time of exposure not only on the excess risk, but also on the baseline risk. The background rate of breast cancer was modeled as a parametric function of city (c), in city status (n), reproductive status (r), attained age (a), and age at exposure (e). Subjects who were not in either Hiroshima or Nagasaki ATB (NIC) were included in all analyses, and the background rate models were stratified by NIC status. Therefore, the NIC group did not add information toward the estimation of the background rate but did contribute information on the variation of the rates by age at exposure and attained age. The log background rate was modeled as a linear function of city, logarithm of attained age, a piecewise quadratic function of age at exposure joining smoothly at ages 30 and 50 years, and reproductive status. A simpler model in which the log baseline rate was linear in attained age was also used. Reproductive status was modeled using indicator vari-

ables $I(r = 2)$ and $I(r = 3)$, which give 2 degrees of freedom (df) for heterogeneity among the three categories.

The ERR was modeled as a linear function of dose, $\text{ERR}(d, a, e, r) = \beta d \gamma(e, a, r)$ in which $\gamma(\cdot)$ describes the modifying effects of the covariates. The effect modification model is parameterized so that the βd corresponds to the dose effect for a woman exposed to radiation at age 30 years ($e = 30$) and with an attained age of 70 years ($a = 70$). Although this parameterization extrapolates the age effects outside of the range of observed ages ATB for women in the premenarche reproductive status group, we used this parameterization to compare our results to those most commonly presented in previous publications of data from this cohort (10, 13).

Additive models were also fit to investigate breast cancer incidence. These additive models took the form

$$\lambda_{d,c,n,a,e,r} = \lambda_0(c, n, a, e, r) + \text{EAR}(d, a, e, r)$$

in which $\text{EAR}(\cdot)$ is the excess additive risk (EAR). The background rate of breast cancer in the additive model was the same as in the ERR model. EAR was modeled using a linear function of dose: $\text{EAR}(d, a, e, r) = \beta d \gamma(a, e, r)$. For both the ERR and EAR models, dose effect modification was modeled as

$$\gamma(e, a, r) = \exp\{\theta_e(e-30) + \theta_a \ln(a/70) + \delta_2 I(r = 2) + \delta_3 I(r = 3)\}.$$

This allowed reproductive status to modify the radiation dose effect in a categorical manner. To test the primary hypothesis that the risk of breast cancer differed depending on a woman's reproductive status ATB, models constrained to have no effect of reproductive status on the background and/or excess risk (that is, with $\delta_2 = 0$ and $\delta_3 = 0$) were compared with those in which the constraint was relaxed.

To investigate the possibility of confounding by known breast cancer risk factors, we also used a model that controlled for reproductive risk factors including age at menarche (m), age at first birth (b), and number of births (p) in the baseline model rather than modeling the reproductive status categories directly. These models took the form

$$\lambda_{d,c,n,a,e,r,m,b,p} = \lambda_0(c, n, a, e, m, b, p)[1 + \text{ERR}(d, a, e, r)]$$

and

$$\lambda_{d,c,n,a,e,r,m,b,p} = \lambda_0(c, n, a, e, m, b, p) + \text{EAR}(d, a, e, r)$$

for the ERR and EAR models, respectively. However, as described below, the addition of reproductive risk factors to the baseline risk did not improve the fit of the model beyond the model accounting for heterogeneity between reproductive status categories, and data from these models are not reported.

The Poisson regression models described above were fit using Epicure software (17). Differences between models in which the risk of breast cancer depended on dose, age at exposure, and attained age, and those models in which the risk was further modified by reproductive

Table 1. Descriptive characteristics by reproductive status category of the female LSS and AHS cohorts with radiation dose, who were not diagnosed by death certificate or autopsy, and who were not pregnant ATB (*n* = 60,978)

Characteristic	Reproductive status ATB			
	Premenarche (<i>n</i> = 9,128)	Between menarche and first birth (<i>n</i> = 7,149)	Post first birth (<i>n</i> = 13,836)	Missing (<i>n</i> = 30,865)
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Age ATB (y)				
0-9	6,277 (68.7%)	— (0.0%)	— (0.0%)	5,177 (16.8%)
10-19	2,850 (31.2%)	3,945 (55.2%)	94 (0.7%)	5,722 (18.9%)
20-29	(0.0%)	2,564 (35.9%)	3,575 (25.8%)	4,072 (13.2%)
30-39	— (0.0%)	467 (6.5%)	5,179 (37.4%)	4,385 (14.2%)
40-49	— (0.0%)	173 (2.4%)	3,677 (26.6%)	5,202 (16.9%)
≥50	— (0.0%)	— (0.0%)	1,311 (9.5%)	6,307 (20.4%)
City				
Hiroshima	6,652 (72.9%)	5,257 (73.5%)	11,163 (80.7%)	19,656 (63.7%)
Nagasaki	2,476 (27.1%)	1,892 (26.5%)	2,673 (19.3%)	11,209 (36.3%)
Distance from hypocenter (meters)				
NIC	1,462 (16.0%)	1,326 (18.6%)	2,797 (20.2%)	8,939 (29.0%)
≥3,000	1,921 (21.1%)	1,634 (22.9%)	2,963 (21.4%)	6,885 (22.3%)
<3,000	5,745 (62.9%)	4,189 (58.6%)	8,076 (58.4%)	15,041 (48.7%)
Breast dose (Gy)				
<0.05	4,090 (44.8%)	3,663 (51.2%)	7,077 (51.2%)	19,524 (63.3%)
0.05-0.49	4,420 (48.4%)	2,800 (39.2%)	5,855 (42.3%)	9,765 (31.6%)
0.50-0.99	348 (3.8%)	354 (5.0%)	541 (3.9%)	903 (2.9%)
1.00-1.99	193 (2.1%)	239 (3.3%)	238 (1.7%)	443 (1.4%)
≥2.0	77 (0.8%)	93 (1.3%)	125 (0.9%)	230 (0.8%)
Age at menarche (y)				
>16	1,365 (13.9%)	849 (10.8%)	2,823 (23.9%)	571 (27.2%)
15-16	2,980 (30.4%)	2,788 (35.6%)	5,326 (45.1%)	876 (41.7%)
13-14	4,576 (46.7%)	3,603 (46.0%)	3,339 (28.3%)	587 (28.0%)
≤12	886 (9.0%)	599 (7.6%)	317 (2.7%)	66 (3.1%)
Missing	— (0.0%)	413 (5.0%)	3,472 (22.7%)	28,765 (94.3%)
Age at first birth (y)*				
<20	393 (5.1%)	358 (5.9%)	3,022 (22.0%)	187 (5.1%)
20-24	4,161 (53.7%)	3,009 (50.0%)	8,271 (60.1%)	1,652 (44.9%)
25-29	2,717 (35.0%)	1,869 (31.0%)	1,983 (14.4%)	1,453 (39.5%)
≥30	485 (6.3%)	786 (13.1%)	477 (3.5%)	384 (10.5%)
No. of births				
Nulliparous	38 (0.5%)	326 (5.2%)	— (0.0%)	415 (7.0%)
1-2	5,658 (73.5%)	3,726 (59.6%)	3,335 (25.2%)	3,024 (50.7%)
3-4	1,891 (24.6%)	1,937 (31.0%)	4,982 (37.7%)	1,815 (30.4%)
>4	112 (1.5%)	267 (4.3%)	4,896 (37.1%)	709 (11.9%)
Missing	1,429 (15.7%)	893 (12.5%)	623 (4.5%)	24,902 (80.7%)

NOTE: Percentages shown for missing data for a given variable are based on the total number of people in that category, whereas those shown for nonmissing values are based only on those with known data.

*Among parous women.

status were tested using likelihood ratio tests. Ninety-five percent confidence intervals (CI) were calculated by Wald's method for parameters in exponential terms and by the profile likelihood method for dose-response parameters β .

Ethical considerations

The conduct of the LSS was approved by the Human Investigation Committee of RERF. The use of death certificates of the LSS subjects was approved by the Ministry of Internal Affairs and Communications. The respective

committees of Hiroshima City Cancer Registry, Hiroshima Prefecture Tissue Registry, and Nagasaki Prefecture Cancer Registry approved the use of cancer registry data for the present study.

Results

During the 904,078 migration-adjusted person-years of follow-up accumulated between 1958 and 2002, a total of 641 breast cancer cases meeting the criteria for inclusion were diagnosed in 30,113 cohort members who could be classified by reproductive status. At the time of the bombing 9,128 (30%) women were premenarche; 7,149 (24%) were between menarche and a first birth; and 13,836 (46%) were post-first birth. Table 1 describes these women and the 30,865 in the LSS and AHS cohort who were not excluded by the criteria above but for whom reproductive status could not be determined. A higher percentage of women between menarche and first birth ATB received high doses of radiation, with 4.6% of women in this reproductive status group receiving a dose of ≥ 1 Gy compared with only 2.9% of women who were premenarche and 2.6% of women who were post-first birth. Women who were post-first birth ATB tended to have older ages at menarche and younger ages at first birth compared with women in either the premenarche or between menarche and first birth reproductive status groups. Specifically, nearly 70% of women who were post-first birth ATB were 15 years or older at menarche compared with 46.4% of women between menarche and first birth ATB, and 44.3% of women premenarche ATB. Over 80% of women who were post-first birth ATB were ages < 25 years at their first birth, whereas fewer than 60% of women in the premenarche or between menarche and first birth groups were ages

< 25 years at their first birth. Women between menarche and a first birth were much more likely to be nulliparous (5.2%), compared with women who were premenarche ATB (0.5%).

Compared with women who could be classified into one of the three reproductive status groups, women who were not included in the analyses of breast cancer risk because of missing data tended to be older ATB; 20.4% were ≥ 50 years of age ATB. Women with missing data were also more likely to be NIC and have a radiation dose estimate < 0.05 Gy, compared with women in each reproductive status category.

To investigate the primary hypothesis of dose effect modification by reproductive status, the baseline risk of breast cancer was first modeled to depend on an individual's city of residence, age ATB, and attained age, as previously described. Overall, the relative risk (RR) increased with increasing radiation dose, and the ERR associated with a 1-Gy increase in radiation exposure was 1.55 (95% CI, 0.87-2.42) for a woman who was age 30 years ATB and reached an attained age of 70 years (Table 2). In this linear ERR model, the ERR/Gy is allowed to vary as a function of age ATB and attained age. However, neither the observed 3% (95% CI, -31 to 36%) decrease in risk with each decade increase in age at exposure (age ATB) nor the decrease in proportion to the 0.78th power of attained age (95% CI for exponent of attained age: -2.4 to 0.9) significantly affect the ERR/Gy. The estimated EAR was 12.64 cases per 10,000 person-year-Gy, again for age 30 years ATB and attained age 70 years. A significant decrease in EAR with each decade increase in age ATB of 43% was observed (95% CI, -57 to -26%). On the additive scale, the risk of breast cancer increased in proportion to the 2.8th power of attained age (95% CI, 1.7-3.9).

Table 2. Breast cancer risk and radiation exposure: baseline depends on city, in-city status, age ATB, and attained age

Overall: all reproductive status categories combined				
Dose category (Gy)	Subjects	Person years	Cases	RR (95% CI)*
<0.005	14,830	443,966	261	1.00 (Reference)
0.005-0.49	13,075	397,345	266	1.19 (1.00, 1.49)
0.50-0.99	1,243	36,102	54	2.42 (1.70-3.43)
1.00-1.99	670	18,968	40	3.33 (2.19-5.00)
≥ 2.00	295	7,694	20	4.33 (2.61-6.08)
ERR per Gy ($e = 30, a = 70$)				1.55 (0.87-2.42)
Age at exposure (% $\Delta/10$ -y increase)				-3% (-31 to -36%)
Attained age (power)				-0.78 (-2.4 to -0.9)
EAR per Gy ($e = 30, a = 70$)				12.64 (8.18-17.72)
Age at exposure (% $\Delta/10$ -y increase)				-43% (-57 to 26%)
Attained age (power)				2.8 (1.7-3.9)

*95% CI calculated from the profile likelihood for hazard ratios and ERR and EAR per Gy terms and from Wald's method for age at exposure and attained age terms.

Table 3. Dose effect modification: baseline depends on city, in-city status, age ATB, and attained age

	<u>Premenarche</u> RR (95% CI)*	<u>Between menarche and first birth</u> RR (95% CI)*	<u>Post-first birth</u> RR (95% CI)*
ERR model			
ERR/Gy ($e = 30, a = 70$)	1.31 (0.36-3.58)	2.36 (1.12-4.13)	1.1 (0.41-2.70)
Age ATB [†]		0% (-39 to 63%)	
Attained age [†]		-0.64 (-2.3 to 0.97)	
EAR model			
EAR/Gy ($e = 30, a = 70$)	9.56 (2.91-24.6)	19.10 (10.02-31.0)	2.82 (1.71-3.92)
Age ATB [†]		-44% (-64 to -13%)	
Attained age [†]		2.82 (1.71-3.92)	

*95% CI calculated from the profile likelihood for hazard ratios and ERR and EAR per Gy terms and from Wald's method for age at exposure and attained age terms.

[†]Age ATB (change/decade) and attained age (power) effects assumed equal for all reproductive status ATB categories.

When the radiation-associated excess risk of breast cancer was allowed to vary by reproductive status as in Table 3, marginally significant effect modification was observed based on likelihood ratio tests for the significance of the categorical excess risk per Gy terms (ERR: $\chi^2 = 6.04$, $df = 2$, $P = 0.049$; EAR: $\chi^2 = 7.09$, $df = 2$, $P = 0.029$). Using age 30 years ATB and attained age 70 years as a common point of reference for purposes of comparison, women between menarche and first birth have an ERR (2.36/Gy; 95% CI, 1.12-4.13) nearly twice as large as the ERR of women who were premenarche (1.31/Gy; 95% CI, 0.36-3.58) and women who were post-first birth (1.10/Gy; 95% CI, 0.41-2.07; Table 3). Similar dose effect modification was observed in the EAR model with 19.01 (95% CI, 10.02-31.0) excess breast cancer cases per 10,000 per person-year

per Gy in women between menarche and a first birth, compared with an excess of only 9.56 (95% CI, 2.91-24.60) among premenarchal women and 2.82 (95% CI, 1.71-3.92) among post-first birth women.

To investigate this dose effect modification further, we sought to account for possible heterogeneity in the baseline risk of breast cancer between reproductive status groups. Allowing the baseline risk of breast cancer to vary with reproductive status, in addition to city, age ATB, and attained age, significantly improved the fit of the models (ERR: $\chi^2 = 16.8$, $df = 2$, $P < 0.001$; EAR: $\chi^2 = 15.1$, $df = 2$, $P < 0.001$). The addition of reproductive status to the baseline model, while improving overall fit, did not substantially change the overall radiation-associated risk of the simpler model that did not include reproductive status in the baseline model. Specifically, the overall ERR

Table 4. Breast cancer risk and radiation exposure: baseline depends on city, in-city status, age ATB, attained age, and reproductive status ATB

Dose category (Gy)	Overall: all reproductive status categories combined			
	Subjects	Person-years	Cases	RR (95% CI)*
<0.005	14,830	443,966	261	1 (Reference)
0.005-0.49	13,075	397,345	266	1.21 (0.99-1.48)
0.50-0.99	1,243	36,102	54	2.62 (1.93-3.57)
1.00-1.99	670	18,968	40	3.64 (2.57-5.16)
≥ 2.00	295	76,934	20	4.83 (3.03-7.70)
ERR per Gy ($e = 30, a = 70$)				1.44 (0.79-2.29)
Age at exposure (% $\Delta/10$ -y increase)				-0.05 (-33 to 34%)
Attained age (power)				-0.81 (-2.5 to 0.87)
EAR per Gy ($e = 30, a = 70$)				12.13 (7.65-17.20)
Age at exposure (% $\Delta/10$ -y increase)				-0.44 (-57% to 26%)
Attained age (power)				2.8 (1.7-3.9)

*95% CI calculated from the profile likelihood for hazard ratios and ERR and EAR per Gy terms and from Wald's method for age at exposure and attained age terms.

Table 5. Dose effect modification: baseline depends on city, NIC status, age ATB, attained age, and reproductive status ATB

	Premenarche	Between menarche and first birth	Post-first birth
	RR (95% CI)*	RR (95% CI)*	RR (95% CI)*
ERR model			
ERR/Gy ($e = 30, a = 70$)	1.07 (0.22-3.62)	1.36 (0.54-2.75)	1.53 (0.63-2.90)
Age ATB [†]		-15% (-52 to 51%)	
Attained age [†]		-0.78 (-2.4 to 0.88)	
EAR model			
EAR/Gy ($e = 30, a = 70$)	7.74 (1.89-21.91)	14.3 (6.44-25.37)	11.1 (5.13-18.55)
Age ATB [†]		-5% (-69 to -18%)	
Attained age [†]		2.76 (1.66-3.87)	

*95% CI calculated from the profile likelihood for hazard ratios and ERR and EAR per Gy terms and from Wald's method for age at exposure and attained age terms.

[†]Age ATB (change/decade) and attained age (power) effects assumed equal for all reproductive status ATB categories.

per Gy when reproductive status was included in the baseline model was 1.44 (95% CI, 0.79-2.29; Table 4), compared with 1.55 (95% CI, 0.87-2.42) when it was not. More strikingly, the variation in risk across the reproductive status categories was no longer present when reproductive status was incorporated into the baseline model. Neither the ERR nor the EAR model showed evidence of statistically significant dose effect modification by reproductive status (ERR: $\chi^2 = 0.25$, $df = 2$, $P = 0.88$; EAR $\chi^2 = 2.7$, $df = 2$, $P = 0.26$; Table 5).

All analyses were repeated excluding women who were older than 50 years ATB in an effort order to exclude women who were likely to be postmenopausal at the time of exposure. The results of the analyses excluding these older women did not differ significantly from the analyses presented above (data not shown). All analyses were also repeated excluding nulliparous women to examine whether the results were due to an effect of timing of exposure or an effect of parity. The results of these analyses excluding nulliparous women did not differ significantly from the analyses presented above (data not shown). In addition, we modeled the length of the interval between menarche and a first pregnancy (in years) in the background rate of breast cancer (data not shown). However, doing so did not improve the model fit beyond controlling for reproductive status. To investigate the robustness of the results to the background models, we also used categorical representations of age ATB and attained age in the background model in place of the continuous forms of age ATB and attained age, which did not markedly affect the results (data not shown). Finally, a model was fit in which the modifying effects of age at exposure and attained age were allowed to differ for each reproductive status group, but again, this model did not substantially improve the fit of the model in which there was a single modifying effect for age at exposure and attained age.

Discussion

This is the first article to use the atomic bomb survivor cohort to examine whether the interval between menarche and a first pregnancy is a particularly sensitive period in a woman's life in relation to the risk of radiogenic breast cancer. The well-defined LSS and AHS cohort provides an important source of data to address this issue.

After accounting for significant heterogeneity in the baseline risk of breast cancer among women in different reproductive status groups, we did not observe a significant difference in the risk of breast cancer among women exposed to radiation between menarche and a first pregnancy compared with women exposed either before menarche or after a first birth. Although we did not observe the anticipated effect modification by reproductive status, we did observe a significant association between being in this sensitive window ATB and the baseline risk of breast cancer. In models in which the baseline risk of breast cancer was taken to depend on reproductive status, compared with women who were premenarchal ATB, women between menarche and a first birth ATB had a 37% (95% CI, 0-88%) higher background risk of breast cancer, and women who were after first birth had a 10% reduced risk of breast cancer compared with the premenarche ATB group (data not shown). This association between reproductive status and the baseline breast cancer was independent of the radiation effect.

It is likely that women with longer intervals between menarche and first birth had a higher probability of being between menarche and first birth at the time of exposure. This can be thought of as a type of wait time bias, whereby women with a longer interval have a higher probability of being sampled at any given time than women with a shorter interval. In addition to wait time bias, the length of the interval between menarche and first birth may be longest for women who were between menarche

and first birth ATB as a consequence of the war. Given the clear biological evidence that this window is relevant because of the susceptibility of undifferentiated breast tissue (5, 6), women with a longer interval between menarche and first birth would be expected to have a higher baseline risk of breast cancer. This would contribute to the observed significance of reproductive status on the baseline risk of breast cancer in our results.

Further, it is likely that radiation induces breast carcinogenesis to some extent regardless of timing of exposure given the increased radiation-associated risk at all ages of exposure, noted in our results and those of previous studies (10, 11, 13). Although the timing of menarche and first birth may be associated to breast cancer risk through the effect of endogenous hormones on undifferentiated breast tissue, the pathway by which radiation causes damage may be independent and less affected by these reproductive milestones. This may explain why statistically significant dose effect modification by reproductive status was observed only when reproductive status was not included in the baseline risk, and that upon accounting for heterogeneity across reproductive status groups by adding it to the baseline risk model, the dose effect modification was no longer significant.

Our estimates of the radiation associated breast cancer risk are generally consistent with the estimates given in the most recent incidence report on solid cancers in the atomic bomb survivors (13). Our hypothesis was that women exposed to radiation between menarche and first birth will have a higher radiation-related breast cancer risk than women exposed at the same age but outside of this interval. Thus, it refers to an effect that can operate in addition to the age ATB effect. Therefore, our findings are not necessarily inconsistent with the observed early-onset effect described by Land et al. (10). Comparing our overall ERR and EAR results to that report, the combined effects of radiation, age ATB, and attained age are similar, as evidenced by the overlapping CIs. However, our estimate of 12.64 cases per 10,000 person-years per Gy (95% CI, 8.18-17.7) is somewhat larger than the estimate of 9.2 cases per 10,000 person-years per Gy (95% CI, 6.8-12.0). This suggests that the effect of radiation on an additive scale may differ in this subset of women from both the LSS and AHS with complete data on reproductive status, compared with the entire cohort used in the incidence analysis. The higher ERR and EAR estimates observed in this study, compared with studies using the entire female LSS cohort, may be due in part to the younger overall age of this subcohort.

This study has several limitations. Unlike articles on breast cancer incidence in atomic bomb survivors that include the entire female LSS cohort, this study was limited to women with available data on reproductive status ATB. Of the 70,146 women in the LSS cohort, only 44,024 completed at least one LSS questionnaire or AHS clinical exam. Between missing data and our exclusion criteria, the

number of women available for analysis was reduced to 30,113. Insofar as this subset of women with complete data differed from the cohort as a whole, the results presented here may not be generalizable to all female atomic bomb survivors. We attempted to investigate the differences between women included in the analysis and those who were excluded due to missing data on reproductive status. The main difference between those included and those with missing reproductive status information was that the excluded women tended to be older ATB. We did not attempt to assign women with missing data to a reproductive status category based solely on their age ATB because we felt that doing so might bias the results. However, the data that we do have on the 30,865 women excluded because of missing data on reproductive status, and not due to other prespecified exclusions, described in Table 1, suggest that there are no systematic differences between excluded and included women.

Other limitations unique to using data from the LSS and AHS cohort are important to consider in the interpretation of our results. Although we used the latest dosimetry developed for this cohort, there is a degree of uncertainty in the estimated breast dose received by each subject. This uncertainty in dose estimation is likely to be nondifferential, resulting in a bias toward the null. Given our null result, we cannot rule out the possibility that dose effect modification exists but we were unable to detect it because of this uncertainty in dose estimation. It is also possible that by including only those women with data on reproductive status, this study captures a subset of LSS and AHS members with a higher radiation dose than the cohort as a whole. This surveillance bias is a result of more complete data ascertainment from women exposed to higher radiation doses. This potential bias could explain the differences in our radiation-associated risks compared with those reported by Preston et al. (13).

The analyses of Preston et al. (13) and Land et al. (8) about breast cancer incidence in atomic bomb survivors and the recent study of Walsh et al. (18) highlight the fact that estimates of age-dependent radiation-related risks can be quite sensitive to the choice of model for the effects of birth cohort and age on background risk. However, our estimates of radiation-related risks as functions of reproductive status at exposure did not change markedly when we replaced the preferred parametric background model with a model that treated age ATB and attained age as categorical variables, suggesting that our findings are unlikely to be biased by misspecification of the background age effects.

Finally, this study had limited power to detect effect modification by reproductive status. For example, when reproductive status was included in the baseline model, the EAR among women between menarche and first birth was nearly double that of women who were premenarchal at the time of the bombing, but the CIs of these two estimates overlapped considerably. Using data from the entire female LSS and AHS cohorts, we estimated

that we would have 80% power to detect an effect modification factor of ~ 2.4 . However, we only had data on a subset of the population used to calculate study power. Whereas we expected $\sim 1,073$ breast cancer cases, we only had 641 cases that could be classified by reproductive status, reducing the study power considerably. Our negative results do not conclusively rule out the possibility of dose effect modification of smaller magnitude that might nevertheless be of biological importance.

In summary, although we found evidence of dose effect modification by reproductive status, this effect disappeared when we accounted for the heterogeneity in the baseline breast cancer risk between reproductive status groups. This suggests the possibility that radiation exerts similar carcinogenic effects on the breast regardless of its stage of differentiation pointing to the potency of radiation as a breast carcinogen.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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