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A case-control interview study of breast cancer among Japanese A-bomb survivors. I. Main effects

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Women with breast cancer (cases = 196) and without the disease (controls = 566), selected from the Life Span Study sample of A-bomb survivors and nonexposed residents of Hiroshima and Nagasaki, Japan, and matched on age at the time of the bombings, city, and estimated radiation dose, were interviewed about reproductive and medical history. A primary purpose of the study was to identify strong breast cancer risk factors that could be investigated further for possible interactions with radiation dose. As expected, age at first full-term pregnancy was strongly and positively related to risk. Inverse associations were observed with number of births and total, cumulative period of breast feeding, even after adjustment for age at first full-term pregnancy. Histories of treatment for dysmenorrhea and for uterine or ovarian surgery were associated positively and significantly with risk at ages 55 or older, a finding that requires additional study. Other factors related to risk at older ages were the Quetelet index (weight [kg]/height [cm]^2) at age 50, history of thyroid disease, and hypertension. Neither age at menarche nor age at menopause was associated significantly with risk. Subjects appeared to be poorly informed about history of breast cancer or other cancer in themselves or in their close relatives; this finding suggests that innovative strategies maybe required when studying familial cancer patterns in Japanese populations. *Cancer Causes and Control* 1994, **5,** 157-165

Key words: Atomic bomb survivors, breast cancer, Japan, reproductive history.

Introduction

Increased breast cancer risk is a well-documented effect of radiation exposure among female survivors of the atomic bombings, in August 1945, of Hiroshima and Nagasaki, Japan. First shown by Wanebo *et al,*[1] who reported 27 incident cases during 1950-66 in the clinical subsample of survivors solicited for regular biennial examinations at the Atomic Bomb Casualty Commission, it was demonstrated subsequently in successive incidence surveys by McGregor *et al*[2] and Tokunaga *et al*[3-5] based on the larger Life Span Study

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(LSS) sample[6] which is the principal basis for studies of A-bomb survivors at the Radiation Effects Research Foundation (RERF) in Japan. The most recent of these studies,[5] which covered the period 1950-85, found 807 cases of breast cancer among some 70,000 women of all ages at the time of the bombings (ATB).

Several findings with respect to radiation-related risk, notably a tendency for dose-specific relative risk (RR) to decrease strongly with increasing age ATB and to remain fairly constant, for fixed age ATB, over time following exposure, raise questions about factors affecting breast cancer risk in this special population. Does the LSS cohort appear similar to other studied populations of women with respect to the influence of well-known epidemiologic risk factors, or are there important differences? Are epidemiologic factors associated with increased risk of breast cancer generally also associated with greater susceptibility to radiation-induced breast cancer? Finally, does the excess risk of breast cancer following exposure to ionizing radiation specifically depend upon the physiological state of the exposed woman at the time of exposure, *e.g.*, on her reproductive history at that time?

To address these questions, an interview study was undertaken of living cases and controls residing in the cities and environs of Hiroshima and Nagasaki. A major aim of the study was to investigate the interaction of radiation dose and other risk factors in the causation of breast cancer. A study design was used in which cases and controls were matched on radiation dose as well as age and city of residence. This approach was feasible because all the information about risk as a function of radiation dose that might have been obtained through a case-control study was already available, or became available later, from cohort-based incidence studies.[3-5] One of these, covering the period 1950-74, was conducted before the cases and controls were selected; later, coverage was extended through 1980 and 1985. The present report, the first based on the case-control study, is concerned with identifying main-effect factors other than radiation, and describing their associations with breast cancer risk. In this analysis, radiation dose plays no role except that of a potential confounding factor whose influence has been controlled by matching. Possible interactions of the main-effect factors with radiation dose are discussed separately.[7]

Materials and methods

Cases

At the time of selection, 360 incident cases of breast cancer had been identified in the (then) most recent incidence survey,[3] and another 113 more recent cases were found in the LSS tumor registry,[8] for a total of 473. Two hundred and twenty-nine cases were found to be deceased, and the addresses of 13 living cases were outside the Hiroshima-Nagasaki area. A total of 29 cases (10 percent of the remainder) could not be interviewed due to refusal (24), inability to make contact (four), or senility (one). Interviews were obtained from the remaining 202 cases, six of whom were later determined not to be breast cancer and therefore excluded, leaving a total of 196 cases for the present analysis.

Controls

Controls (*n* = 566), matched to the interviewed cases by city, age ATB (± 24 months), exposure class (non-exposed, exposed with a specific dose estimate, or exposed but without a dose estimate), and estimated breast-tissue dose, were selected from among the LSS cohort members then resident in the two cities. A variable matching ratio was used in order to maximize information relevant to interaction with radiation dose: four controls were selected if the case had a tissue-dose greater than 0.5 Gy or was from Nagasaki; otherwise, two controls were selected.

Relatively few (nine percent) of the potential controls contacted refused to be interviewed, and in most cases ill health was given as the reason. The percentage of controls found to reside outside the contacting area (six percent) was approximately the same as for the cases. Controls unavailable for interview were replaced by other controls satisfying the matching criteria.

Interviews

Cases and controls were interviewed in their homes, places of business, or in the RERF clinic, by RERF public health nurses. The interview questionnaire covered the following general areas: (i) reproductive history, including age at menarche, age at last menses, age at first marriage, and history of deliveries, pregnancies, and breast feeding; (ii) history of treatment for tuberculosis (including pneumothorax), hypertension, diabetes, thyroid disease, or breast disease; (iii) history of cancer and family history of breast cancer; (iv) height and weight at age 20, and weight at age 50; and (v) medical treatment for infertility, menstrual irregularities, menopausal disorders, or to prevent abortion, surgery or radiation treatment of the uterus and/or ovaries and related chemical or hormone therapy, and use of oral contraceptives (OC).

Other sources of information

For most of the subjects, and nearly all of the cases, information was available on many of the questionnaire items from clinical records and data acquired in previous surveys and studies, including (for some) a case-control study by Nakamura *et al*[9] using breast cancer cases diagnosed through 1969; such information was used in the analysis mainly as a check on the accuracy of the interview responses, but occasionally to fill in an unclear or omitted response. Age at menopause was determined by interview, and cases were classified as premenopausal or postmenopausal by comparing age at diagnosis with age at last menses. However, menopausal ages also were checked against clinical information at RERF, which tended to be available more often for cases than for controls. For case-control sets with age at diagnosis before age 45, ages at second and later deliveries were obtained from RERF records or by telephone follow-up, to avoid including in the analysis information on births and lactation among the controls after the age of breast cancer diagnosis in the matched case.

Statistical analysis

Indicator, continuous, and categorical variables were defined as appropriate, and used as independent regression variables in univariate and multivariate, conditional, logistic analyses for retrospective case-control data with variable matching ratios.[10,11] Because matching by dose and age ATB was not exact, parallel analyses were carried out in which these matching variables were included as covariates. The results of the adjusted analyses were only trivially different from those of the corresponding analyses without covariates, however, and are not presented. Significance testing was by likelihood ratio test between pairs of hierarchical models;[10,11] the 'deviance' statistic, defined as twice the natural logarithm of the ratio of maximized likelihoods, is assumed to have a null distribution distributed approximately as chi-square with degrees of freedom equal to the number of additional parameters in the more general model. Odds ratios (OR) were used as the measure of RR. Likelihood-based confidence intervals (CI) were calculated at the 95 percent level, and *P* values are two-tailed.

Results

Age at last menses could not be determined for one case. Of the remainder, 41 percent were classified as premenopausal and 59 percent as postmenopausal at diagnosis. Study cases were diagnosed between 1955 and 1981, at ages ranging from 28 to 78. Age ATB ranged between one and 50, and age at interview between 37 and 87.

Univariate analyses

Averages of matched-set means (or percent positive) for cases and controls, and a summary of univariate, linear, logistic regression analyses, are given for selected variables in Table 1. For each variate, the table shows the estimated OR with a CI and the corresponding *P* value for the null hypothesis (OR = 1). The table also gives the number of informative matched sets

Table 1. Summary of univariate logistic regression analyses for selected variables

Risk factor	Mean (% positive)		OR[a]	(CI)[b]	Dev[c]	***P***
	Cases	Controls				
Age at menarche	14.5	14.6	0.95	(0.85-1.06)	0.9	0.34
Age at menopause	45.7	45.1	0.98	(0.93-1 .04)	0.4	0.54
Age at 1st full-term pregnancy	25.5	24.1	1.09	(1.04-1.13)	15.2	0.001
Number of deliveries	1.99	2.65	0.79	(0.71-0.88)	20.4	0.001
Cumulative lactation (yr)	1.42	2.02	0.78	(0.69-0.87)	19.4	0.001
Height at age 20 (cm)	152	152	0.99	(0.96-1.02)	0.5	0.48
Quetelet index[d] at age 50	22.8	21.7	1.11	(1.01-1.23)	4.5	0.034
Thyroid disease	5.2	3.7	1.58	(0.71-3.29)	1.3	0.25
Hypertension	19.1	14.3	1.37	(0.85-2.18)	1.7	0.19
Benign breast disease	5.2	4.9	1.11	(0.49-2.34)	0.1	0.80
Cancer other than breast	2.6	0.9	2.64	(0.72-9.63)	2.2	0.14
Breast cancer in mother, sister, or daughter	2.5	2.1	1.16	(0.36-3.16)	0.1	0.79
Treatment for dysmenorrhea	7.3	3.3	2.28	(1.08-4.76)	4.7	0.031
Gynecologic surgery	22.8	12.1	1.97	(1.28-3.01)	9.5	0.002

[a]OR = estimated odds ratio multiplier per unit increment in each variable.
[b]CI = 95% confidence interval.
[c]Dev = deviance reduction (approximately chi-square with 1 degree of freedom) *cf* the null hypothesis (OR = 1.00).
[d]Weight (kg)/height (cm)^2.
[e]Diagnosed >1 yr prior to breast cancer diagnosis.

contributing to each analysis, *i.e.*, those sets in which at least one control was different from the case. All variables correspond to ages prior to diagnosis in the case. If menopause occurred at an age later than that of diagnosis, age at menopause was treated as a missing variable. Analyses of variables representing disease or medical treatment also were performed for the period five years or more before diagnosis, to avoid the inclusion of events triggered by the breast cancer itself; there were no findings markedly different from those shown. Other variables, not shown, were either extremely close correlates of tabulated variables or were uninformative for reasons discussed in the text.

General reproductive history

In these data, age at menarche appeared to be unrelated to breast cancer risk. Also, there was no evidence that menopause occurred at older ages among cases than among controls.

Significantly fewer cases than controls had experienced a pregnancy lasting seven months or longer (OR = 0.53); age at first full-term pregnancy, among those who had experienced one, was significantly higher among cases than controls (OR multiplier per year of age was 1.08). Essentially all the deviance explained by these two variables was explained by a single variable, tabulated in Table 1, in which a default value[12] of 30 years was assigned to women who had never had a full-term pregnancy.

Cases had significantly fewer children prior to breast cancer diagnosis than their controls, corresponding to an OR multiplier of 0.79 per child. Cumulative period of lactation (OR= 0.78 per year) explained virtually all of the deviation indicated by variables related to lactation (ever breast fed, number of breastfed children, and average lactation period per delivery). The same was true of number of breastfed children; either could have been chosen as representative of the group of lactation variables.

Medical history other than gynecologic

Cases and controls did not differ significantly with respect to reported height, weight, or Quetelet index (weight [kg]/height [cm]^2; QI) at age 20. Risk (after age 50) was significantly related to QI at age 50, but not to weight at age 50. For risk at all ages, there was no difference by history of tuberculosis or pneumothorax therapy for tuberculosis, diabetes, thyroid disease, hypertension, or cancer other than breast cancer.

History of breast disease other than cancer yielded a somewhat surprising result: most reported diagnoses among cases (128/138) were at ages less than two years prior to breast cancer diagnosis as determined from clinical records. Cases and controls did not differ with respect to reported breast disease at ages more than one year younger than that of breast cancer diagnosis (Table 1). No case, and no control, reported that her mother had breast cancer; 14 subjects reported breast cancer in a sister and three in a daughter, with no difference between cases and controls either before or after adjustment for numbers of family members at risk.

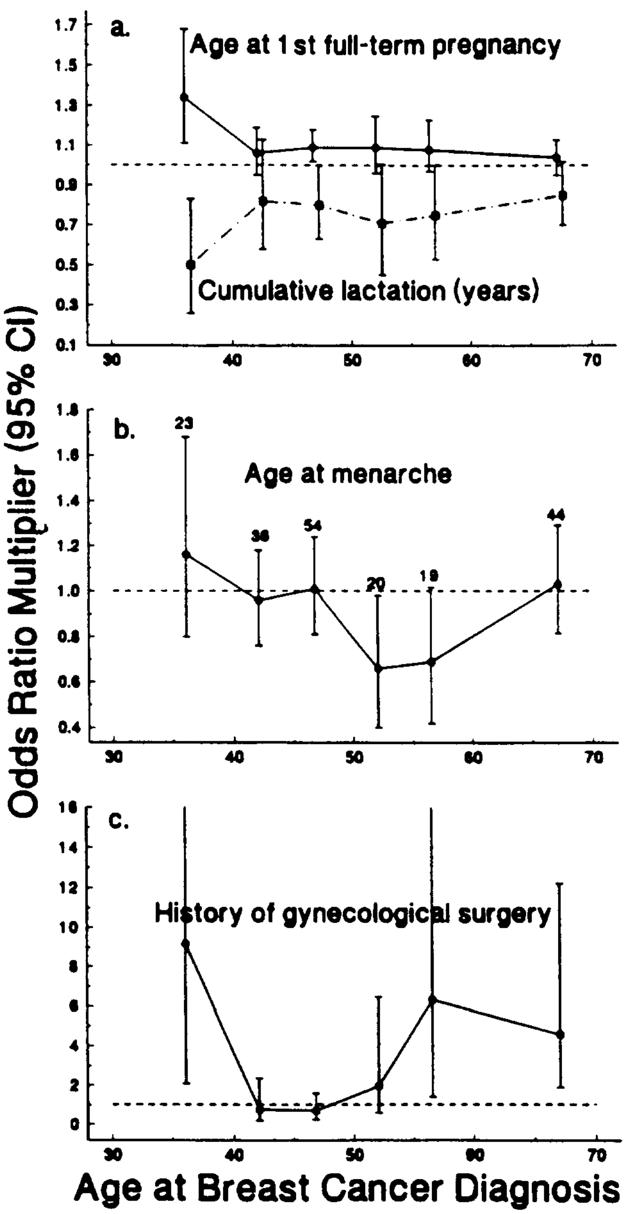

Figure 1. Estimated odds ratio multiplier per unit increment, with 95% confidence intervals; for selected variables by age at diagnosis (< 40, 40-44, 45-49,..., >= 65). Horizontal placement of points corresponds to the average age at diagnosis in each interval. Number of cases is given above each confidence interval in b.

History of gynecologic treatment

Significantly more cases than controls had histories of treatment for menstrual problems (OR = 2.3, CI = 1.1-4.8, *P* = 0.03). The result was the same if treatment within five years before cancer diagnosis was disregarded. Use of OCs was very infrequent.

Significantly more cases than controls reported having received uterine or ovarian surgery (OR= 2.0, CI = 1.3-3.0, *P* = 0.002). A similar pattern was observed for operations five or more years before breast cancer diagnosis. ORs did not depend markedly upon whether the operations were reported to have occurred around the time of menopause, or earlier or later. Nearly half of the respondents reporting gynecologic surgery said that all of the uterus was removed, and about 25 percent of them reported bilateral oophorectomy. There is, however, some reason to doubt the accuracy of these reports; over one-fourth of operations involving bilateral oophorectomy were reported to have occurred one or more years before menopause, and 46 percent of operations reported not to have included bilateral oophorectomy occurred within one year of the reported age at menopause. It seems likely that the operations occurred, but that the details tended not to be well understood by the patients. X-ray or other radiation treatment of the uterus and ovaries was very rare (three cases and five controls), and was not associated significantly with subsequent breast cancer risk.

Age at diagnosis

OR estimates and CIs were calculated for selected variables by age interval (< 40, 40-44, 45-49, 50-54, 55-59, and 60+); graphs for four variables are shown in Figure 1. These analyses were motivated by suggestions that certain risk factors may have reversed effects before and after age 40,[13,14] and by the possibility that some factors might be more important for risk at young or old ages. A statistically significant difference was found between ORs for age at first full-term pregnancy before and after age 40 (*P* = 0.02), and suggestive differences were found for number of births (*P* = 0.06) and cumulative lactation (*P* = 0.08); however, these were differences in degree, not direction. The graph for number of births, not shown, was closely similar to that for cumulative lactation **(a).** Tests for trend with increasing age were nonsignificant for all variables, with the exception of history of treatment for thyroid disease (not shown) which was associated more strongly with risk at older ages (*P*= 0.05). As shown in **b,** the expected protective effect for late age at menarche was observed only for risk between ages 50 and 60. Evidence of an excess risk associated with gynecologic surgery was found for risk before age 40 and after age 55, but not otherwise **(c).** Finally, statistically significant excess risks associated with histories of hypertension (OR = 2.0, CI = 1.0-3.8, *P* = 0.04) and thyroid disease (OR = 5.0, CI = 1.3-23.7, *P* = 0.02) were observed for risk after age 55, but not before.

Premenopausal cf *postmenopausal risk*

As might be expected from the findings by age at diagnosis, age at first full-term pregnancy, number of births, and cumulative lactation were associated more strongly with premenopausal than postmenopausal risk, whereas the opposite was true for histories of hypertension, thyroid disease, treatment for dysmenorrhea, and gynecologic surgery (Table 2). The differences in ORs were statistically significant for hypertension and gynecologic surgery, suggestive for

Table 2. Premenopausal *cf* postmenopausal breast cancer risk: summary of univariate logistic analyses for selected variables

Risk factor	Premenopausal risk		Postmenopausal risk		Difference *P* value
	OR[a]	(CI)[b]	OR[a]	(CI)[b]	
Age at 1st full-term pregnancy	1.12	(1.04-1.21)	1.07	(1.02-1.12)	0.26
No. deliveries	0.72	(0.58-0.88)	0.82	(0.73-0.93)	0.27
Cumulative lactation (yr)	0.65	(0.51-0.82)	0.83	(0.73-0.95)	0.07
Age at menarche	1.02	(0.85-1.22)	0.92	(0.79-1.05)	0.36
Hypertension	0.19	(0.01-0.95)	1.85	(1.10-3.13)	0.006
Thyroid disease	0.89	(0.14-3.45)	2.01	(0.78-4.92)	0.35
Dysmenorrhea	1.56	(0.32-6.02)	3.01	(1.22-7.62)	0.43
Gynecologic surgery	0.62	(0.22-1.46)	3.23	(1.92-5.50)	0.001

[a] OR = estimated odds ratio multiplier unit increment in each variable.
[b] CI = 95% confidence interval.

cumulative lactation, and nonsignificant for the other variables just mentioned. Age at menarche was unrelated to either premenopausal *(P* = 0.85) or postmenopausal risk *(P*= 0.21).

Bivariate and multivariate analyses

Selected logistic analyses were conducted to adjust one variable for one or more others. Analyses were performed within two groups: age at first full-term pregnancy, number of births, and cumulative period of lactation were in the first group; and dysmenorrhea, gynecologic surgery, QI, thyroid disease, and hypertension in the second. The groupings reflect the results of analyses not shown, that OR estimates, confidence limits, and *P* values were little different between univariate analyses and bivariate analyses involving one variable from each group. Variables in the first group were evaluated with respect to risk at all ages, and those in the second group with respect to risk at ages 55 and older.

Analyses for variables in the first group, before and after adjustment, are shown in Figure 2. Age at first full-term pregnancy was related independently to risk after adjustment for number of children or cumulative lactation period, with *P* values for trend of 0.08 and 0.05, respectively; simultaneous adjustment for both variables yielded virtually the same ORs and CIs as adjustment for number of births alone, but a slightly weaker *P* value *(P* = 0.097). Number of births and cumulative lactation period each were related to risk after adjustment for age at first full-term pregnancy *(P*= 0.03). It is interesting that the adjustment resulted

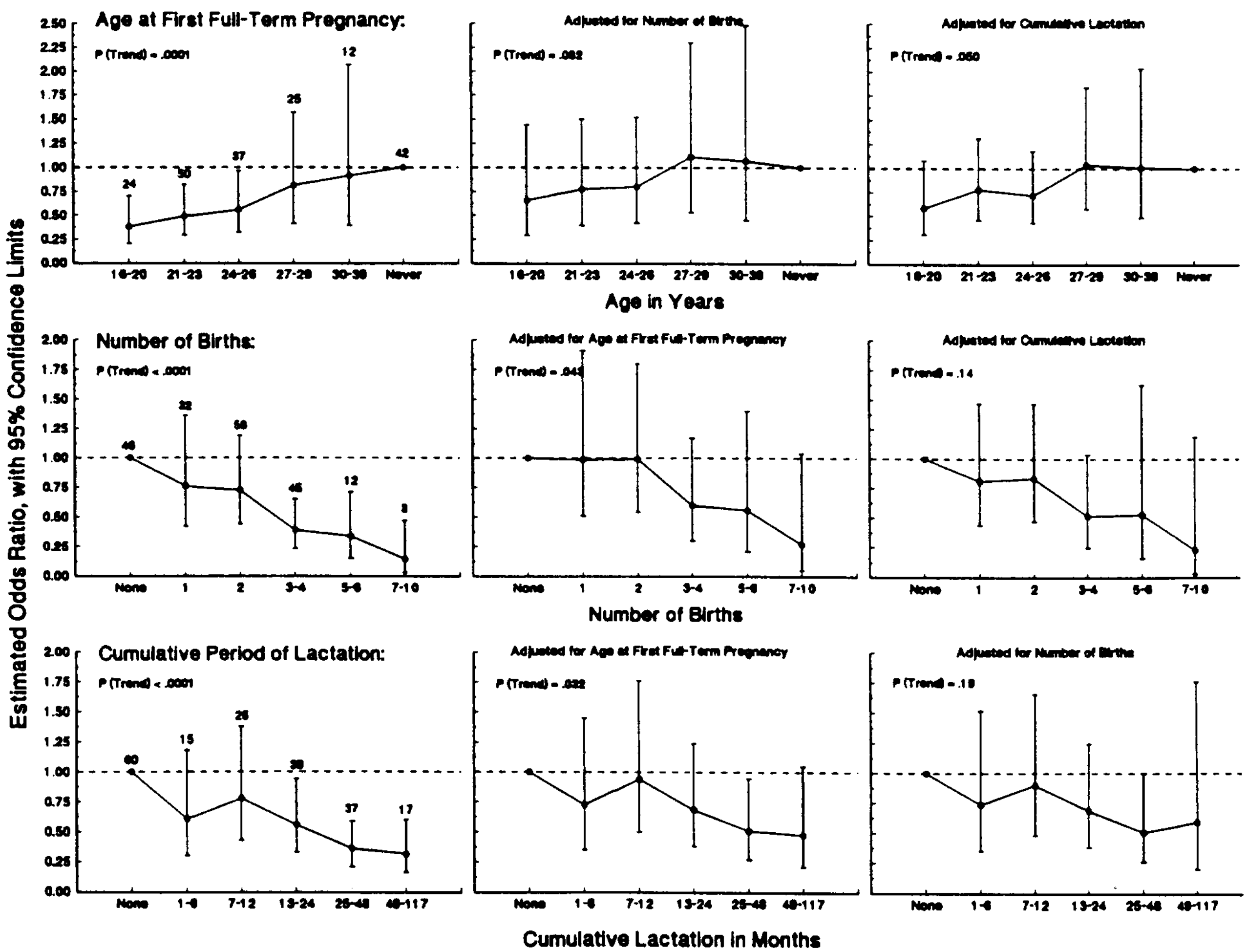

Figure 2. Dose-response curves for three reproductive history variables strongly associated with breast cancer risk: unadjusted, with numbers of breast cancer cases at each factor level (left-most panels); and adjusted for other factors as indicated (center and right-most panels).

in flattening of the curves in regions where the OR estimates were near unity. Number of births and cumulative lactation were sufficiently correlated that adjustment of one for the other resulted in trend *P* values greater than 0.10, and neither approached statistical significance after simultaneous adjustment for the other and for age at first full-term pregnancy.

The results just discussed depend to some extent on the necessarily arbitrary selection of representative variables to be analyzed. An alternative analysis, not shown, was performed in which years of lactation per birth (with a default value of zero for nulliparous women) replaced cumulative lactation. Lactation per birth was associated almost as strongly with risk as cumulative lactation in a univariate analysis (OR = 0.5 per year, CI = 0.3-0.7, *P* = 0.001) and, in combination with age at first full-term pregnancy and number of births, the deviance reduction was the same as that obtained with cumulative lactation and the other two variables. With the alternative model, however, a different (apparent) hierarchy emerged: *P* values for age at first full-term pregnancy, number of births, and lactation per birth, each after adjustment for the other two, were 0.14, 0.064, and 0.44, respectively. Thus, in the alternative parameterization, number of births appeared to be the most important variable, and length of lactation per birth the least.

A history of hypertension was not an independent predictor of risk at ages 55 or older, after adjustment for dysmenorrhea, gynecologic surgery, QI, or thyroid disease. For the latter variables, OR estimates, confidence intervals, and *P* values were little affected by bivariate model adjustment.

Discussion

The present investigation was a necessary first stage in a study of possible modifying factors in the induction of breast cancer by exposure to ionizing radiation received from the Hiroshima and Nagasaki A-bombs. It is, therefore, somewhat different from most other case-control studies because its main purpose was to characterize breast-cancer risk factors in a unique population, valuable as a source of information on radiation-related cancer risk, and only incidentally to investigate risk relationships applicable to more general populations.

For the present, we are concerned with placing the first-stage results in the context of findings from a large number of epidemiologic investigations of breast cancer in other populations. That literature has been covered in detail by several comprehensive review articles.[12,15-19] The most consistently observed risk association—that with age at first full-term pregnancy or age at first delivery-was confirmed in the A-bomb survivor population, with ORs similar to those reported elsewhere.[12] The association held for risk at all ages, both premenopausal and postmenopausal. No single factor, however, explained all of the variation in risk associated with reproductive history. Number of births and cumulative lactation were significantly and negatively associated with risk, in approximately linear relationships. Adjustment for age at first full-term pregnancy minimized the reduction in risk for women with one or two children, but the decline in RR with higher numbers remained marked and statistically significant. Thus, the present study is in agreement with several studies reporting an independent protective effect of multiple births.[19] The finding for cumulative lactation is in substantial agreement with Yoo *et al*[20] for a Japanese population and Byers *et al*[21] and McTiernan and Thomas[22] from studies of American populations. Cumulative lactation and number of births were not independently related to risk. Other reproductive history variables were identified which might be more accessible to investigators in an expanded study. For example, age at first birth and number of births are more easily available than age at first full-term pregnancy and cumulative lactation, especially in a study not confined to living cases and controls; yet, in the present study, the two pairs of variables explained about the same amount of information.

This study differed from many others in that no association was found with age at menarche or age at menopause. It is possible that errors in recall may have been partly responsible for these findings, although most subjects interviewed appeared to be confident of their ability to recall age at menarche, in particular, and independent confirmation from clinical records of age at menopause was obtained for most cases and many controls. In an earlier case-control study based on the LSS population, Nakamura[9] obtained a nonsignificant RR before age 50 of 2.8 for menarche at age 13 or younger. That finding was not duplicated in the present study, which found a possible association with age at menarche only for risk between ages 50 and 60.

For risk after age 50, two-thirds of Nakamura's cases, but only one-fourth of controls, who had experienced natural menopause had stopped menstruating before reaching age 50 (OR = 0.2, *P* = 0.027), a result opposite to that usually found. Yoo *et al,*[20] in a hospital-based study, found a nonsignificant, increasing trend in risk of postmenopausal cancer with increasing age at menopause, but no clear relationship of risk with age at menarche. Thus, it is conceivable that, among Japanese, age at menarche and age at menopause are not related strongly to risk. If, for example, exposure to endogenous estrogens is somehow a lesser breast-cancer risk factor among Japanese compared with Western women, one might expect the length of the interval between menarche and menopause also to be less important. Another complicating factor is that, among Nagasaki survivors, age at natural menopause has been reported recently to be associated negatively with radiation dose.[23] Although our cases and controls were matched on dose, about 20 percent of cases were radiation induced, according to cohort-based incidence data,[6] and it is conceivable that sensitivity to induction of breast cancer and depression of ovarian function by radiation might be correlated.

Given the general lack of other studies in which associations with thyroid disease and hypertension have been reported,[17] and the fact that Japan is not an endemic goiter area, it is not possible to assign any great importance to the weak associations with risk in this study. The positive association of the QI at age 50 with subsequent risk appears generally consistent with a positive correlation, reported especially in Western populations, between obesity and postmenopausal breast cancer,[25,26] although in fact, obesity was rare in our study. Another possibility is an associated survival advantage, since the study was restricted to living cases, many of whose diagnoses occurred five, 10, or more years prior to interview.

Family history of breast cancer, which is among the factors most strongly associated with risk in Western populations, was reported too rarely in this generally low-risk population for an association to be found. It seems likely that subjects were not well informed about cancers of the breast or of any other site among their relatives. Cultures vary as to the specificity of communication between physician and patient about the diagnosis of cancer,[27] and anecdotal and other evidence[28-30] suggests that Japanese cancer patients traditionally have not been fully informed about their diagnoses. The present data include some direct evidence in support of this view, in that breast cancer cases tended to identify their cancers as benign breast disease, and subjects almost surely underreported instances of breast cancer among their mothers.

The observed positive associations of risk with treatment for dysmenorrhea and, at ages 55 and older, with uterine and ovarian surgery are difficult to explain, but are consistent with at least one other study of breast-cancer risk factors in Japan.[31] History of gynecologic treatment was not a primary focus of the study, and no effort was made to confirm reported treatment with physicians or hospitals. The most likely explanation is that the patients were not precisely informed about their treatment. On the other hand, positive associations of breast cancer risk with hysterectomy were observed in recent case-control studies in Fukuoka[31] and Shanghai;[32] in the latter report, the authors presented evidence indicating that the association might be due to confounding with socioeconomic status.

One of the lessons of the present study is that it appears to be difficult to determine details of medical history in a Japanese population, including history of cancer in the subject or his or her relatives, by relying solely on interviews. In that respect, a hospital-based approach like that of Yoo *et al*[20] and Hirohata *et al*[31] has a number of advantages. For A-bomb survivor studies, which must be population based, alternative sources of information, like clinical records and matches with tumor registries, seem desirable despite the extra effort their use may entail.

The experience of the A-bomb survivor population has included not only the atomic bombings but also changes typical of urban Japan as a whole. Japanese breast cancer rates are among the lowest in the world, but age-adjusted mortality increased 50 percent between 1953-57 and 1983-87,[33] perhaps in response to changes in lifestyle including nutrition and reproductive norms.

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