Risk Factors for Breast Cancer According to Family History of Breast Cancer

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For the Nurses' Health Study Research Group

Background: **Family history of breast cancer is an established risk factor for this disease and is used to identify women at higher risk, although the impact of risk factors for breast cancer among women with a family history is not well defined.** ***Purpose:*** **Using a modified extended log-incidence Pike model, we prospectively examined the impact of risk factors for breast cancer among women with and without a family history of the disease.** ***Methods:*** **Data analyzed were obtained prospectively from the Nurses' Health Study. Two thousand two hundred forty-nine incident cases of invasive breast cancer were identified in a cohort of 89 132 women aged 30-55 years in 1976 followed biennially through 1990 (1.1 million person-years of follow-up). With the use of proportional hazards models, we evaluated the association between risk factors for breast cancer and risk among women with and those without a family history of the disease. We then fit a modified extended log-incidence Pike model to these data.** ***Results:*** **Among women with a family history of breast cancer, reproductive risk factors had associations that were different from those observed among women without a family history of the disease. In particular, we observed little protection from later age at menarche, no protection from multiple births when compared with nulliparity, nor from early, as compared with later, age at first birth. Fitting these data to a model of breast cancer incidence on the basis of reproductive risk factors, we observed an adverse effect of first pregnancy on risk of breast cancer among women with a family history of breast cancer that was approximately 50% greater in magnitude than among women without a family history. Additional births after the first birth conveyed little protection for women with a family history. History of benign breast disease, past use of oral contraceptives, and use of postmenopausal hormones showed relative risks that did not differ between women with a family history and those without a family history of the disease.** ***Conclusions:*** **We observed a consistent increase in risk of breast cancer among women with a mother or sister history of the disease that was exacerbated by first pregnancy. Among women with a family history of breast cancer, the adverse effect of pregnancy persisted so that to age 70 years, parous women were at higher risk of breast cancer than nulliparous women. Among women without a family history of the disease, first pregnancy was associated with a smaller increase in risk, and early pregnancy and higher number of births were each associated with reduced breast cancer incidence. [J Natl Cancer Inst 1996; 88:365-71]**

Family history of breast cancer is an established risk factor for this disease and is used to identify women at higher risk, although the impact of risk factors for breast cancer among women with a family history is not well defined (*1*). We demonstrated that an extended mathematical model of breast cancer incidence, incorporating age at menarche, age at first birth, spacing of children, and age at menopause, adequately describes the breast cancer incidence rates in the Nurses' Health Study. In this model, first birth is associated with a transient (temporary) increase in risk followed by a subsequent decrease in risk (*2*). This transient increase in risk with first pregnancy was confirmed subsequently (*3*). Animal data also show differentiation of the breast tissue at the time of the first birth (*4*) and lower susceptibility to carcinogens after the first birth (*5*). Because women with a family history of breast cancer may inherit genetic changes that alter their risk of breast cancer, reproductive events and other established risk factors may influence risk of breast cancer differently among women with and without a family history of breast cancer.

Few prospective data are available that specifically address the contribution of breast cancer risk factors among women with a family history of breast cancer. We compared the risk factors among women with a family history of breast cancer and among women with no family history of breast cancer during 14 years of follow-up among participants in the Nurses' Health Study. We previously reported that for women in this cohort, a family history of breast cancer in either their mother or sister is associated with a relative risk of 1.8 (95% confidence interval [CI] = 1.5-2.0) compared with those women with neither mother nor sister diagnosed with breast cancer (*1*). Overall, in this cohort, approximately 6% of breast cancer cases are attributable to a family history in a first-degree relative. With the use of a modified extended log-incidence Pike model [*see* companion report; (*6*)], we prospectively examined the impact of risk factors for breast cancer among women with and without a family history of breast cancer.

Methods

The Nurses' Health Study cohort was established in 1976 when 121 700 female registered nurses 30-55 years of age completed a mailed questionnaire that included items about known or suspected risk factors for cancer and cardiovascular diseases. Baseline information included details of breast cancer risk factors (*7,8*). Every 2 years, follow-up questionnaires have been mailed to the women to update the information on breast cancer risk factors and to ascertain whether major medical events have occurred.

Data on Family History

A history of breast cancer in the mother or sister was elicited on the 1976 questionnaire. This information included whether the mother was still living, and, if so, age at diagnosis; if the mother was deceased, her age at death and diagnosis of breast cancer. We also inquired about the number of sisters

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See "Notes" section following "References."

and whether any had been diagnosed with breast cancer. Information on maternal and sister history of breast cancer (yes/no) was updated in 1982 and again in 1988. We used these data to divide the cohort into those women who had a positive family history of breast cancer in either mother or sister and those with no family history in a first-degree relative.

Data on Other Risk Factors

Age at menarche was reported on the base-line questionnaire. Information on other risk factors for breast cancer, including parity, age at first birth, history of benign breast disease, and menopause was reported on the base-line questionnaire and updated every 2 years based on responses to the follow-up questionnaires. We last updated parity on the 1984 questionnaire. We classified a woman as postmenopausal from the time she returned a questionnaire on which she reported natural menopause or hysterectomy with bilateral oophorectomy. Self-report of menopause is highly reproducible in this cohort and is valid with regard to details of the extent of ovarian surgery (*9*). In addition, we classified women reporting hysterectomy without bilateral oophorectomy as postmenopausal at the age when natural menopause had occurred in 90% of the cohort (54 years for current cigarette smokers and 56 years for nonsmokers). Among postmenopausal women, we recorded the use of replacement hormone therapy in 1976 and updated this use every 2 years, allowing classification of women as current users, past users, and never users of replacement hormones (*10*). Lifetime use of oral contraceptives was recorded on the base-line questionnaire allowing calculation of duration of use and determination of current and past use and was updated every 2 years to 1984 (*7*).

In 1980, we first assessed dietary intake, including vitamin A intake, and history of usual alcohol consumption over the past year. Data were reported on intake of beer, wine, and liquor and an estimate of total alcohol intake was calculated. This measure of alcohol consumption is reliable when compared with 28 days of diet records (*11*).

Identification of Breast Cancer Cases

On each questionnaire, we inquired whether breast cancer had been diagnosed and, if so, the date. All women who reported breast cancer (or the next of kin for decedents) were contacted for permission to review the relevant hospital records and confirm the self-reported diagnosis. Pathology reports were obtained for 93% of the cases, and information on histologic tumor type, tumor size, and node involvement was extracted by physicians blinded to data on family history and other risk factors reported by the participants. We omitted from analysis the small number of carcinomas in situ.

Population for Analysis

We excluded from the analysis all women who reported breast or other cancer (excluding nonmelanoma skin cancer) on the 1976 questionnaire; of these, 105 406 women returned the 1978 questionnaire. We further excluded 4205 women because their number of pregnancies reported in 1976 was different by two or more children from the estimated number of pregnancies in 1976 based on reported ages of children in 1978. We excluded another 6993 women whose number of living children as derived from the reported ages differed from their parity in 1978. We also further excluded 2757 women whose number of living children in 1978 was less than their reported number of children in 1976. In addition, we excluded 412 women whose age at first birth estimated from the reported children in 1978 was greater than 3+ the age at first birth reported in 1976. Also, we excluded 768 women whose age at menarche was either unknown or was reported to be less than or equal to 8 years or greater than or equal to 22 years. Further exclusions included unknown parity (n = 199), age at any birth greater than age at menopause (n = 677), and women reported to be nulliparous in 1976 whose age of oldest child was greater than 2 years in 1978 (n = 201) and whose age at menopause was unknown (n = 52). We also excluded 10 women whose age at death was unknown. This left a total cohort of 89 132 women eligible for follow-up. During the 14 years of follow-up from the return of the 1976 questionnaire to May 31, 1990, we accrued 1 148 593 person-years of follow-up; 2249 incident cases of invasive breast cancer were identified among these women. Follow-up of the cohort for the identification of nonfatal breast cancer was conducted by mailed questionnaires with telephone interview or certified mailings to nonrespondents; together, these follow-up procedures and responses accounted for 94% of potential person-years. For fatal breast cancer, follow-up was more than 98% complete (*12*).

Statistical Analysis

The primary analysis, conducted separately among women with a family history and among women without a family history of breast cancer, used incidence rates with person-months of follow-up as the denominator. For each participant, person-months were allocated according to the 1976 exposure variables and were updated according to information on follow-up questionnaires. Family history was updated in 1982. For women who developed breast cancer or died, person-months were assigned according to the covariate status reported on the most recent completed questionnaire, but follow-up terminated with the diagnosis of breast cancer or death.

We used relative risk (RR) as a measure of association, defined as the incidence of breast cancer among women who had a risk factor (e.g., history of benign breast disease) divided by the corresponding rate among women who had no such history. We used proportional-hazards models to adjust for multiple risk factors simultaneously (*13*). All *P* values are two sided.

Mathematical Model

To confirm the findings from the traditional epidemiologic analysis for reproductive risk factors on the basis of incidence rates and multivariate logistic regression, we fitted a refinement of the extended Pike model (*2*) to women with a family history and separately to women without a family history. [*See* Appendix for model specification and the accompanying paper by Rosner and Colditz for a detailed discussion (*6*)]. During examination of goodness of fit for the extended breast cancer model, we observed that the model slightly overpredicted incidence for early age at first birth among women under age 45 years and underpredicted incidence for late age at first birth among women over age 54 years. Therefore, we modified the model to allow for the immediate increase in risk with first birth to increase with age. We retained terms that incorporate age at menarche, age at menopause, the effect of spacing of births, and the increase in risk at first birth. Furthermore, we separated the effect of pregnancies into the premenopausal period and the postmenopausal period on the basis of model fitting. Goodness-of-fit results indicate that the modified extended Pike model provides a better fit. We compared the coefficients for the model fitted to women with a positive family history of breast cancer with those with no family history of breast cancer (*2*).

Results

In 1976, 4.6% of women reported that their mother had been diagnosed with breast cancer, 1.5% reported that at least one sister had been diagnosed, and 0.1% reported that both mother and sister had breast cancer. The incidence of breast cancer increased with age among both women with a positive family history of breast cancer and women with no family history of breast cancer (Fig. 1). Reproductive risk factors showed weaker associations among women with a positive family history of breast cancer compared with women with no family history of breast cancer. These differences were most noticeable among postmenopausal women (data not shown). Compared with women reporting menarche before age 12 years, the RR adjusted for age, parity, age at first birth, age at menopause, history of benign breast disease, past use of oral contraceptives, and use of postmenopausal hormones for those with menarche at age 15 years was 0.75 (95% CI = 0.62-0.92) for women with no family history of breast cancer and 0.90 (95% CI = 0.55-1.49) for women with a positive family history of breast cancer (Table 1).

Parity and age at first birth both showed different associations among women with a positive family history of breast cancer and women with no family history of breast cancer. Compared with nulliparous women, increasing parity was associated with decreasing risk among women with no family history of breast cancer, but this trend was less clear among women with a positive family history of breast cancer (Table 1). Among women with a positive family history of

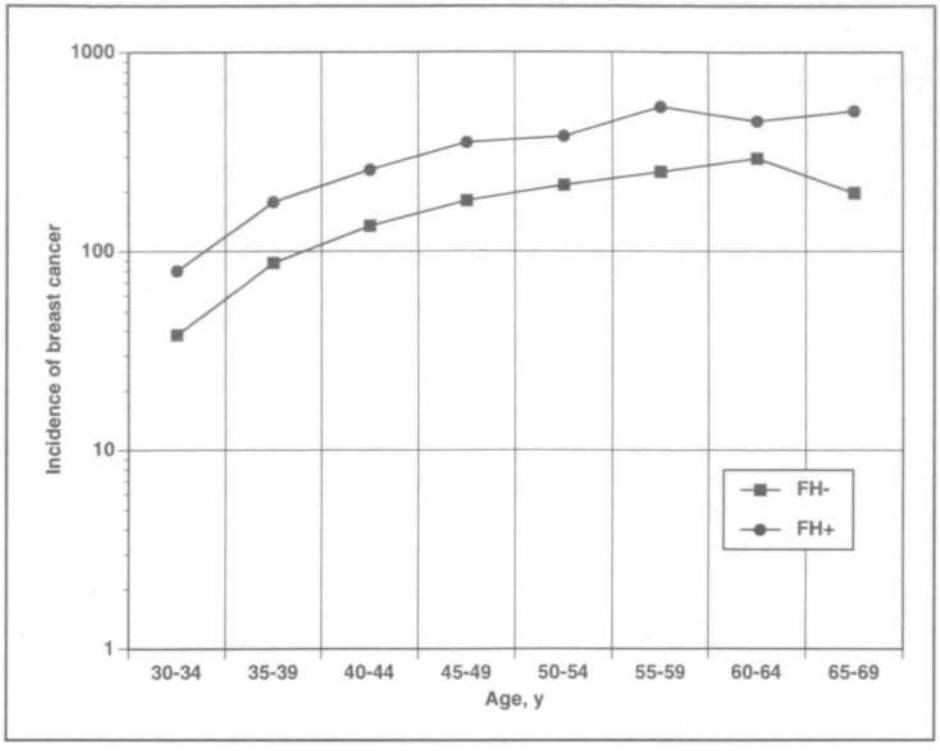

Fig. 1. Incidence of breast cancer per 100 000 women according to age and family history.

breast cancer, risk of breast cancer was elevated at each level of parity versus nulliparous. Increasing age at first birth showed a weak positive relation among women with no family history of breast cancer, most noticeably among women with parity 2 and parity 3. In contrast, all levels of age at first birth had a higher RR compared with nulliparous women with a positive family history of breast cancer than the comparable RR for women with no family history of breast cancer.

Among postmenopausal women, age at menopause showed a stronger relation with risk of breast cancer among women with no family history of breast cancer than among women with a positive family history of breast cancer. Compared with menopause before age 47 years, women with menopause after age 51 years had an RR that was 1.47 (95% CI = 1.22-1.76) for women with no family history of breast cancer and 1.00 (95% CI = 0.65-1.53) for women with a positive family history of breast cancer.

History of benign breast disease showed a similar RR of breast cancer in each group. Among postmenopausal women, the current use of replacement hormones is associated with increased risk in this cohort (*10*). We categorized duration of use into less than 5 years of use and 5 or more years of use. Among women with no family history of breast cancer, current use of postmenopausal hormones for 5 or more years was associated with a significant increase in risk of breast cancer (RR = 1.34; 95% CI = 1.11-1.60). Duration of use appeared to be less important among women with a positive family history of breast cancer; however, these analyses were based on few cases (Table 1).

Past use of oral contraceptives was not associated with risk of breast cancer in this cohort. Among women with a positive family history of breast cancer and women with no family history of breast cancer, we observed no important variation in the association between past oral contraceptive use and risk of breast cancer. Compared with never users, among women with no family history of breast cancer, users had an RR that was 1.05 (95% CI = 0.95-1.16), and for women with a positive family history of breast cancer the RR was 0.91 (95% CI = 0.70-1.18).

We examined the relation between alcohol intake and risk of breast cancer. The RR compared with never drinkers was 1.25 (95% CI = 1.06-1.48) for women with no family history of breast cancer consuming 15 g or more of alcohol per day and 0.98 (95% CI = 0.62-1.53) for women with a positive family history of breast cancer (data not shown).

Mathematical Models

On the basis of the model of breast cancer incidence, nulliparous women with no family history of breast cancer have a rate of increase in log incidence of breast cancer that is 8.0% per year from menarche to menopause (e^{β_1}). Age at first birth and parity superimpose effects on this underlying incidence rate of breast cancer so that after the first birth the annual rate of increase up to the age at menopause is decreased by 0.3% per birth. The first birth is associated with a one-time increase in the incidence of breast cancer of 23% if the age at first birth is 30 and the age at menarche is 13 (that is, $e^{\beta_3(t_1 - t_0)}$).

Terms in the extended model show that first pregnancy is not followed by decreased risk of breast cancer among women with a positive family history of breast cancer ($\beta_4 = -0.0018$). Furthermore, for women with a positive family history of breast cancer, the term for the increase in risk at first pregnancy is approximately 50% greater magnitude for women with no family history of breast cancer (Table 2) (52% if the age at first birth is 30 years and the age at menarche is 13 years). That is, for women without a family history, risk is increased by 23% after the first pregnancy at age 30 years; for those with a family history and the same age at first birth, risk is increased by 35%.

To help interpret these results, we also calculated the cumulative incidence of breast cancer from age 20-70 years with the use of the multiple births model. For these estimates to be meaningful, our rates must be comparable with those in the general population. We, therefore, compared incidence in the Nurses' Health Study with that reported from the Surveillance, Epidemiology, and End Results (SEER) Program.[1] Overall, during 14 years of follow-up we observed 97% of the expected number of breast cancers. We observed marked differences in the cumulative risk of breast cancer according to family history and number of pregnancies (Table 3). For nulliparous women the risk of breast cancer before age 70 years was 3.0% higher for women with a

Table 1. Age at menarche, age at first birth (AAFB) and parity, age at menopause, history of benign breast disease and exogenous hormone use, and relative risk (RR) of breast cancer: Nurses' Health Study (1976-1990)*

	No family history			Family history		
	No. of cases	Person-years	Adjusted RR (95% confidence interval)	No. of cases	Person-years	Adjusted RR (95% confidence interval)
Menarche, y						
≤11	445	239 065	1.0†	62	19 244	1.0†
12	527	284 837	0.93 (0.82-1.06)	92	22 452	1.19 (0.86-1.66)
13	605	327 753	0.93 (0.82-1.05)	100	25 656	1.14 (0.82-1.57)
14	221	130 323	0.82 (0.69-0.97)	35	10 311	0.88 (0.57-1.36)
≥15	140	82 296	0.75 (0.62-0.92)	22	6712	0.90 (0.55-1.49)
Parity						
Nulliparous	150	69 666	1.0†	16	5816	1.0†
AAFB, ≤24 y						
1	34	16 908	1.10 (0.75-1.61)	4	1392	1.16 (0.39-3.50)
2	178	120 386	0.81 (0.64-1.02)	24	8200	1.30 (0.68-2.49)
3	220	145 652	0.83 (0.67-1.03)	43	10 859	1.66 (0.92-3.01)
≥4	254	169 098	0.72 (0.58-0.89)	44	12 590	1.30 (0.72-2.37)
AAFB, 25-29 y						
1	56	33 860	0.84 (0.61-1.16)	11	2673	1.77 (0.81-3.86)
2	271	155 743	0.91 (0.74-1.12)	45	12 063	1.35 (0.74-2.25)
3	260	126 396	0.97 (0.79-1.20)	37	10 995	1.20 (0.65-2.20)
≥4	214	115 146	0.80 (0.64-1.00)	34	9816	1.20 (0.65-2.24)
AAFB, 30-34 y						
1	58	19 424	1.46 (1.06-2.00)	7	1491	1.48 (0.57-3.83)
2	92	37 318	1.10 (0.84-1.44)	18	3366	1.64 (0.80-3.35)
3	56	20 002	1.12 (0.81-1.56)	9	1701	1.66 (0.70-3.96)
≥4	23	12 495	0.70 (0.44-1.12)	5	1149	1.42 (0.51-3.96)
AAFB, ≥35 y						
1	32	11 002	1.26 (0.85-1.87)	8	892	2.67 (1.08-6.62)
2	28	7718	1.51 (1.00-2.29)	4	1052	1.27 (0.43-3.85)
3	9	2597	1.37 (0.67-2.82)	2	304	1.91 (0.43-8.49)
≥4	3	883	1.47 (0.46-4.63)	0	16	—
Premenopausal	737	526 929	1.34 (1.14-1.57)	96	33 580	1.50 (0.99-2.27)
Postmenopausal						
Age at menopause, y						
≤46	465	264 097	1.0†	79	21 721	1.0†
47-51	462	190 772	1.20 (1.04-1.40)	87	18 451	1.14 (0.81-1.60)
≥52	274	82 476	1.47 (1.22-1.76)	49	9623	1.00 (0.65-1.53)
Benign breast disease						
No	1195	782 181	1.0†	166	53 354	1.0†
Yes	743	282 093	1.64 (1.49-1.81)	145	31 021	1.49 (1.18-1.89)
Postmenopausal hormones						
Current use						
Never	551	255 069	1.0†	100	24 444	1.0†
<5 y	131	62 805	1.00 (0.81-1.20)	27	5463	1.34 (0.87-2.07)
≥5 y	178	58 826	1.34 (1.11-1.60)	26	5578	1.04 (0.66-1.64)
Past use						
<5 y	166	80 590	0.88 (0.73-1.05)	27	7737	0.77 (0.50-1.18)
≥5 y	51	26 655	0.83 (0.62-1.13)	16	2784	1.20 (0.69-2.13)
Oral contraceptive use						
Never	1109	542 697	1.0†	201	47 237	1.0†
Current	22	16 532	1.56 (1.01-2.41)	4	748	2.47 (0.88-6.94)
Past	790	492 842	1.05 (0.95-1.16)	105	35 729	0.91 (0.70-1.18)

*Adjusted for age in 5 years, age at menarche, parity, menopause and age at menopause, history of benign breast disease, use of oral contraceptives, postmenopausal hormones, and follow-up period.
†Referent group.

positive family history of breast cancer (12.7% versus 9.7%). However, among women with only one birth, the risk for women with a positive family history of breast cancer was 5.0% (for one birth at age 20 years) and 5.8% (for one birth at age 30 years) higher than for women with no family history of breast cancer who have a comparable reproductive history. At each age at first birth, these differences became greater for women with multiple births.

Table 2. Parameters from the multiple births model fitted to women with and without a family history of breast cancer

Coefficient	No family history	Positive family history
α constant	−9.729	−8.584
β_0 increase from birth to menarche (*P*)	0.047 (<.005)	0.047 (.26)
β_1 increase from menarche to menopause for nulliparous women (*P*)	0.082 (<.001)	0.0602 (<.001)
β_2 annual increase in risk after menopause (*P*)	0.0497 (<.001)	0.0365 (.01)
β_3 increase in risk due to first birth (*P*)	0.0124 (<.005)	0.0178 (.13)
β_4 decrease in risk per unit of birth index, before menopause (*P*)	−0.0038 (<.001)	−0.0018 (.48)
β_5 decrease in risk per unit of birth index among postmenopausal women (*P*)	0.00026 (.040)	−0.00010 (.73)
Log likelihood*	−13 930.92	−2027.76

*Log likelihood for the overall breast cancer incidence model = −16 000.76. The difference in −2 log likelihood for family history-specific model versus overall model = 2 log L_1 + 2 log L_2 − 2 log L = 84.16 ~ χ^2_7, P<.001, where L = likelihood for model based on overall dataset and L_1, L_2 = likelihood for women with positive family history or no family history, respectively.

To test the hypothesis that the family history-specific models provided a better fit than the overall model, based on the entire data set, we compared the overall log likelihoods of the respective models. This is more appropriate than comparing specific coefficients because of the interdependence between parameter estimates for different coefficients of the same model. We found that the difference in −2 log likelihood for the family history-specific model versus the model based on the entire data set = 84.16 χ^2_7, P<.001. Thus, this provides a rationale for studying family history-specific models for breast cancer incidence.

Discussion

In this prospective study, we observed a consistent increase in the risk of breast cancer among women with a mother or sister with a history of breast cancer that was exacerbated by first pregnancy. Among postmenopausal women with a positive family history of breast cancer, the adverse effect of pregnancy persisted so that to age 70 years, parous women were at higher risk of breast cancer than nulliparous women. In contrast, among women with no family history of breast cancer, first pregnancy was associated with a smaller increase in risk; early pregnancy and higher number of births were each associated with reduced breast cancer incidence. However, the adverse effect of early menarche was reduced among women with a positive family history of breast cancer.

While previous studies have addressed the relation between family history and risk of breast cancer, most have used retrospective data that may distort the prevalence of family history among cases compared with controls. Floderus et al. (*14*) compared the reporting of family history of breast cancer by twin members with cancer to that reported by their cotwins. They observed a 50% excess reporting of family history of breast cancer by affected twins, which approximates the magnitude of recall bias introduced by differential reporting of family history by cancer patients in a case–control study. The authors noted that this was a conservative estimate, since twins could be in closer contact than siblings in general. The data from the prospective Iowa Women's Health Study show a somewhat lower RR of 1.5 (95% CI = 1.2-1.9) for a family history of breast cancer in a first-degree relative, perhaps related to the older age of that cohort (*15*).

In cross-sectional data from respondents to the 1976 Nurses' Health Study questionnaire, the protective effect of later age at menarche was diminished among women with a family history of breast cancer (*16*). This finding is consistent with several other studies of risk factors among women with and without a family history of breast cancer (*17,18*).

Data from the Iowa Women's Study indicate that reproductive variables are associated differently with breast cancer risk according to family history. Later age at menarche shows a protective effect that is largely limited to women without a family history of breast cancer, and the number of live births was not related to risk of breast cancer among women without a family history. These analyses were based on classification according to age at first birth or parity, and multivariate results were not presented that would account for the correlation between early age at first birth and larger family size (*15*). Data from the Breast Cancer Detection Demonstration Project indicate that risk of breast cancer increases with later age at first birth among women without a family history of breast cancer, but among women with either a maternal history of breast cancer or a sister history, later age at first birth is not associated with a further increase in risk of breast cancer (*19*).

Table 3. Cumulative risk of breast cancer (%) through age 70 years for women with and without a family history of breast cancer, according to age at first birth and at subsequent births

	No family history	Positive family history
Nulliparous	9.7	12.7
Birth at 20 y	9.0	14.0
Births at 20 and 23 y	7.8	13.7
Births at 20, 23 and 26 y	6.9	13.5
Birth at 25 y	9.8	15.2
Births at 25 and 28 y	8.7	15.0
Births at 25, 28, and 31 y	7.9	14.8
Birth at 30 y	10.6	16.4
Births at 30 and 33 y	9.7	16.2
Births at 30, 33, and 36 y	9.0	16.1
Birth at 35 y	11.5	17.6
Births at 35 and 38 y	10.8	17.5
Births at 35, 38, and 41 y	10.3	17.4

Participation rates are high in the present study and similar among women with a positive family history of breast cancer and women with no family history of breast cancer, thereby decreasing the potential for information bias. Thus, loss to follow-up is unlikely to account for any major distortion in this study.

Age, Susceptibility to DNA Damage, and Breast Cancer Risk

The effect of a known carcinogen—radiation—is dependent on age at exposure. Among women, radiation exposure accumulated before age 20 years carries a far higher risk for a given dose than exposure at later ages (*20*). Even radiation before age 10 years carries excess risk for breast cancer (*21*). Lower responsiveness to radiation at later ages suggests that the human breast is less susceptible to carcinogenic effects after pregnancy, which is consistent with the differentiation of mammary tissue in animal models reported by Russo and Russo (*22*).

Increase in Risk Associated With First Pregnancy

Our extended Pike model of breast cancer incidence includes a term for an increase in risk associated with the first pregnancy as suggested by Moolgavkar et al. (*23*). This term would represent the propagation of transformed DNA during the extensive proliferation of breast tissue that occurs throughout the first pregnancy stimulated by high levels of hormones. Animal models show that pregnancy after exposure to carcinogens increases the rate of mammary tumor growth compared with pregnancy before exposure (*24*). In our application of the extended Pike model to the Nurses' Health Study data, this term was significant for the first pregnancy but not for subsequent pregnancies (*2*), suggesting that the breast is protected against the effects of cell proliferation (and the high hormone levels) during second and subsequent pregnancies by the terminal differentiation that occurs during first pregnancy.

The increase in risk of breast cancer associated with first pregnancy is followed by a decrease in the rate of cell turnover and may account for the interaction between age and age at first birth and risk of breast cancer (*25*). This interaction has been observed both in terms of incidence and mortality. Janerich and Hoff (*26*) examined incidence data from New York State, showing a crossover in breast cancer incidence between single and married women at age 42 years, such that married women had higher incidence than unmarried women before this age and lower incidence after it. A similar crossover of incidence has been reported between black and white women in the United States (*27,28*) that is consistent with the distribution of age at first birth by race. Over many decades, black women in the United States have had higher rates of pregnancy and earlier age at first birth than white women (*29*).

The greater magnitude of the adverse effect of first pregnancy among women with a positive family history of breast cancer is consistent with the assumption that a subset of these women inherit genetic changes that are multiplied during cell proliferation of first pregnancy. The adverse effect of first pregnancy would be expected to be stronger among the subset of women with family history who have inherited a genetic predisposition. This group could be defined by both mother and sister history of breast cancer. However, because we have less than 200 participants in this group, it is not possible to fit the model and test this hypothesis.

The similar findings for benign breast disease in women with a positive family history of breast cancer and women with no family history of breast cancer suggest that any molecular changes associated with this risk factor are independent of the genetic alterations inherited by women with a positive family history of breast cancer. In contrast, alcohol appears to act more strongly among women without a family history.

The model of breast cancer incidence offers an important insight into the role of reproductive risk factors on risk of breast cancer. Furthermore, it is consistent with the animal model extensively studied by Russo and Russo (*22*) and indicates that women with a positive family history of breast cancer should not be counseled to have early and repeated pregnancies as a means of reducing their personal risk of breast cancer. Rather, women who undergo such pregnancies appear to be at greater risk.

In conclusion, women with a positive family history of breast cancer should adhere to recommendations for breast cancer surveillance through regular clinical breast examination, breast self-examination, and mammography. Among these women, traditional reproductive risk factors should not be used to predict risk of breast cancer.

Appendix

Revised model of breast cancer incidence, for multiple births:

$$\ln(\text{incidence}) = \alpha + \beta_0 t_0 + \beta_1(t^* - t_0) + \beta_2(t - t_m)m + \beta_3(t_1 - t_0)b_1 + \beta_4 b + \beta_5 b(t - t_m)m,$$

where: t^* = minimum (age, age at menopause); b = birth index = $\Sigma\ (t^* - t_i)b_i$ = total years from each birth to minimum (age, age at menopause) summed over all births in parous women and $b = 0$ for nulliparous women; t_0 = age at menarche; t_1 = age at first birth; t_i = age at ith birth; t_m = age at menopause; t = current age; m = 1 if postmenopausal and 0 if premenopausal; b_1 = 1 if parous and 0 if nulliparous; and b_i = 1 if a woman has $\geq i$ births and 0 otherwise.

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Notes

[1]*Editor's note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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