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Family history and risk of breast cancer: Nurses' Health Study

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Abstract

Background—Family history of cancer remains underused in general clinical practice. We assess age at diagnosis and the role of family history in risk of breast cancer.

Methods—Prospective follow-up of Nurses' Health Study participants from 1980 to 2006. Updated assessment of family history in mother and sister including age at diagnosis. We used youngest age at diagnosis for family member when classifying risk. We confirmed 4327 incident invasive breast cancers confirmed. Breast cancer incidence models fitted to women with and without family history to assess variation in the risk for established risk factors.

Results—Compared to women with no family history those whose mother was diagnosed before age 50 had an adjusted relative risk of 1.69 (95% CI 1.39, 2.05) and those with mother diagnosed at 50 or older had a relative risk of 1.37 (1.22, 1.53). Sister history was associated with increased relative risk; 1.66 (1.38, 1.99) for those with sister history before age 50 and 1.52 (1.29, 1.77) for those with sister diagnosed at age 50 or older. Women with either mother or sister diagnosed before age 50 had a relative risk of 1.70 (1.48, 1.95) significantly higher than those with diagnosis at age 50 or older (RR=1.30; (1.27, 1.54), $p=0.016$). The magnitude of risk associated with established reproductive and lifestyle risk factors did not differ significantly between women with and those without family history with the exception of risk after bilateral oophorectomy in which setting women with family history had greater reduction in risk of subsequent breast cancer.

Conclusion—Women with a family member diagnosed with breast cancer before age 50 had increased risk of breast cancer compared to women with family members diagnosed at older ages. Consistent findings for risk factors regardless of family history adds to robust evidence for risk identification and risk stratification in clinical settings where prevention strategies will apply equally to women with and without family history.

Introduction

Family history of breast cancer remains a major factor that has direct relevance for screening and prevention counseling [1–2]. While very high-risk families require genetic counseling and evaluation for high penetrance genes [3–4], the vast majority of women with family

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history have only one or two relatives with breast cancer, usually diagnosed in mid or later life. How should this family history be classified for clinical practice and risk stratification?

We previously showed in prospective data from the Nurses' Health Study [5] that mother and sister age at diagnosis has a direct relation to the magnitude of risk conveyed through family history. The relative risk decreased with advancing maternal age at time of diagnosis from 2.1 for women whose mother was diagnosed before age 40 to 1.5 for maternal diagnosis after age 70. This finding is largely replicated in the large collaborative reanalysis of breast cancer case-control (n= 44) and cohort studies (n=9), with data drawing largely from the case-control experience (84% of the 58,209 women with breast cancer) and without updates to family history over time in the cohort studies [6]. The relative risk of breast cancer increased with younger age at diagnosis but the association did not differ substantially whether mother or sister was diagnosed with breast cancer. Relative risks were lower in prospective cohorts than from the case-control studies with retrospective recall of family history. [6] In addition, concern persists from some studies suggesting that risk factors may vary between women with family history and those without [7], with possible implications for prevention messages and the overall usefulness of prevention strategies.

To evaluate age at diagnosis in mother and sister and their relation to risk conveyed by positive family history, we evaluated these relations in the extended prospective follow-up of the Nurses' Health Study with more than 4,300 incident invasive breast cancer cases.

Methods

The Nurses' Health Study cohort was established in 1976 when 121,701 female US registered nurses ages 30–55 responded to a mailed questionnaire that inquired about risk factors for breast cancer including reproductive factors, hormone use, anthropometric variables, benign breast disease, and family history of breast cancer. The risk factors have been updated by repeat questionnaires obtained every 2 years up to the present time. [8] Alcohol consumption both currently and at age 18 was ascertained in 1980, as was weight at age 18. Briefly, we excluded women with unknown, inconsistent, or out-of-range reports for height, weight in 1976, or at age 18 years, age at menarche or menopause, or each pregnancy, parity, and duration or type of postmenopausal hormone use as reported previously.[9] In addition, women who underwent a simple hysterectomy were excluded, as were women with prevalent cancers in 1976 or with no follow-up after 1978.

Identification of incident breast cancer cases

On each questionnaire, women were asked whether breast cancer had been diagnosed, and if so, the date of diagnosis. All women (or the next of kin if deceased) were contacted for permission to review their medical records so as to confirm the diagnosis. Confirmed cases of invasive breast cancer from 1980–2006 were included in these analyses. A total of 4327 incident invasive cases of breast cancer were identified among women with complete information on breast cancer risk factors. Overall, 69805 participants remained in the analysis (this included those with family history not missing per table 1). These women contributed 1.6M person-years from 1980 to 2006. This study was approved by the Committee on Human Subjects at Brigham and Women's Hospital.

Exposure: family history

Family history was assessed in 1976 with questions that included:

“Did your mother ever have breast cancer? If yes, at age at first occurrence?”

“Do you have any sisters? If yes, how many? How many of your sisters ever had breast cancer?”

This information on diagnosis of cancer in relatives was updated in 1982, 1988, 1992, and with updates including age at diagnosis for mother and sister in 1996, 2000, and 2004 (<50; 50–59; 60–69; 70+). When classifying family history we used the youngest age of the first family member as the age at diagnosis.

Statistical methods

We estimated mean values for breast cancer risk factors according to family history status using variables reported on or updated to the 1990 questionnaire, or the time period closes for those not assessed on the 1990 questionnaire. We then fit the log-incidence model to the study population and included terms for mothers breast cancer history <50 and mother history 50+; then separately terms for sister history <50 and sister history 50+; and finally family history (mother or sister diagnosed before age 50 and 50+). Finally we fit the models to strata of women defined by family history (no; yes) and compared the models to evaluate associations for terms representing the established reproductive and lifestyle factors related to breast cancer as previously described (see Appendix). [9] Each risk factor was entered one at a time as a cross product term for the risk factor*family history. The parameters of the model are readily interpretable in a relative risk (RR) context. For example, $\exp(-\beta_0)$ = RR for 1-year increase in age at menarche among nulliparous women, $\exp[-(\beta_0 + \beta_2)]$ = RR for 1-year increase in age at menarche among parous women, and so forth.

We modified the family history term in the model to assess the multivariate contribution of the term for maternal history of breast cancer <50; maternal history of breast cancer at age 50 or greater; then sister history <50 and sister history at age 50 or greater.

Results

Prevalence of family history in this cohort

Within the cohort we updated family history and other exposures summarized in Table 1, observing that by 1990, when the youngest women were 44 years of age and the mean age of participants was 56. Overall 15.38% of women reported a family history of breast cancer diagnosed in mother or sister; 3.4% had a family history with first diagnosis before age 50, and 11.94% had first diagnosis at age 50 or older.

We observed no major differences in reproductive risk factors, BMI (current or at age 18), alcohol intake or age at menopause. However women with family history of breast cancer were less likely to be current smokers; and had a higher prevalence of benign breast disease than women with no family history. Among women with a history of breast cancer diagnosed among mother or sister at age 50 or later only 15.9% were current smokers, compared to 18.9% of women with no family history. Among women with family history of breast cancer the prevalence of benign breast disease was substantially higher (47.6% and 45.2%) than among women without family history (37.9%)(Table 1).

Age at diagnosis of mother or sister and risk of breast cancer

We next evaluated the relation between age at family member diagnosis with breast cancer and risk among women in the study. Compared to women with no family history of breast cancer, for women with a positive mother history, those whose mother was diagnosed before age 50 had an adjusted relative risk of 1.69 (95% CI 1.39, 2.05) and those with mother diagnosed at age 50 or greater had a relative risk of 1.37 (1.22, 1.53). The difference between these relative risks was borderline significant, $p=0.06$.

For women with a sister history of breast cancer, the relative risk for those with sisters diagnosed before age 50 was 1.66 (1.38, 1.99) and for those diagnosed at age 50 or older the relative risk was 1.52 (1.29, 1.77). Again this difference in relative risks was not significant, $p=0.43$ (Table 2). Considering the women with either mother or sister diagnosed with breast cancer before age 50, the adjusted relative risk was 1.70 (1.48, 1.95) significantly higher than the relative risk of 1.30 (1.27, 1.54) for those diagnosed at age 50 or older, $p = 0.016$.

To assess the potential variation in magnitude of associations for established risk factors for breast cancer we assessed models for breast cancer incidence in women without a family history and in those with a family history. While the intercept is more than a log unit higher for women with family history (reflecting higher risk from birth that decreases with age), for the established risk factors there was little variation in the magnitude of risk increase (age at first birth), or the protective effect of parity, summarized as the birth index. The adverse effect of first pregnancy defined in the model as age at first birth minus age at menarche, was significant and positive for women with a family history and for those without. The rate of increase in risk per year before menopause was greater in women without family history than for women with family history leading to a narrowing of differences in risk through the premenopausal years. After natural menopause the rate of increase in risk, $e^{(0.0184)}$ was 1.85% increase per year among women with a family history and those without.

Use of postmenopausal hormones has multiple components adding together to define an individual relative risk, for example, a current use term and a duration of use term. For women without family history the relative risk for current users of estrogen plus progestin with 5 years of use is 0.2740 (the current user term) plus $5 * 0.0347$, the increase in risk per year of use, giving $e^{(0.4475)}$ or a relative risk of 1.56. On the other hand for women with a family history the relative risk is $e^{(0.3836 + 5*0.00723)}$ equals a relative risk of 1.52. Considering parity, a postmenopausal woman who has natural menopause at age 50, does not have a history of benign breast disease, never drinks, and is at average height and BMI, and never uses postmenopausal hormones, if she has menarche at age 13 and has four births at ages 20, 23, 26, and 29, then her birth index is 102. This gives a relative risk compared to nulliparous for a woman without family history of $e^{[-(0.0036*102)+(0.0075*7)]} = e^{-0.314} = 0.73$. For a woman with family history the corresponding relative risk compared to a nulliparous woman is $e^{[-(0.00215*102)+(0.00496*7)]} = e^{-0.25402} = 0.78$.

The interaction of established risk factors with family history was further evaluated through assessment of heterogeneity of results presented in table 3. We observed significant heterogeneity for time after bilateral oophorectomy ($p=0.04$). Risk continued to increase more strongly after bilateral oophorectomy among women without family history and showed substantially lower increase in risk for women with family history. Duration of estrogen use was borderline significant ($p=0.076$), with weaker relations among those with family history. No other tests for heterogeneity of associations approached statistical significance.

We also evaluated finer stratifications for age at diagnosis of breast cancer in mother or sister but the relative risks did not differ substantially from the values obtained when groups were combined into less than 50 and 50 or greater. For example, relative risk of breast cancer for mother diagnosed before age 50 was 1.63, for 50–59 it was 1.35 for 60–69 it was 1.31, and for 70+ it was 1.30. Small numbers of cases and the small sample size of the subgroups reduced our ability to meaningfully separate levels of risk in these finer classifications.

Discussion

In this prospective cohort with updated information on family history of breast cancer among mothers and sisters, including age at first diagnosis, we observed that overall 15 percent of women had a positive family history of breast cancer. Women with a family member diagnosed with breast cancer before age 50 carried increased risk for breast cancer compared to women of the same age with family members diagnosed at older ages. Although the prevalence of family history is relatively low it carries a clear and strong increase in risk and provides a marker of risk for clinicians to identify and counsel women – accordingly it is important to see that risk factors for breast cancer appear to operate independent of whether a woman has a family history or does not.

The magnitude of risk due to family history was somewhat lower in our fully adjusted models than reported for the prospective data from the collaborative reanalysis of breast cancer studies.[1] They reported a relative risk of 2.04 (99% CI: 1.72, 2.69) for women with history of breast cancer in relatives before age 50 and 1.50 (1.32, 1.71) for those with relative diagnosed at age 50 or older. This higher risk is likely due to the majority of data being recalled after cancer diagnosis leading to recall bias in case-control studies. However, like that combined analysis, we observed that reproductive and lifestyle risk factors for breast cancer did not alter the risk associated with family history and these risk factors operated to increase and decrease risk regardless of the presence or absence of family history. Although we had previously suggested that among women with family history, the adverse effect of first birth overruled the protective effect of parity, that analysis was based on only 2249 cases of breast cancer.[7] With over 4300 cases and longer follow-up, we now observe that for the combined effect of reproductive factors gives protection from parity among women with family history.

The prospective nature of this study eliminates recall bias. As noted in the collaborative reanalysis of breast cancer studies the retrospective case control studies with recalled family history after diagnosis reported consistently higher relative risk for the case-control studies than the pooled prospective data.[6] Others have studied recall bias and quantified excess reporting of family history among affected family members. [10] Importantly, we updated family history information in this analysis and so provide relative risk estimates more closely aligned with recommendations for real world clinical practice. Concern has been raised about the accuracy of reporting of family history of cancer.[11] However, we note that a recent study shows breast cancer is more accurately reported in family members than other cancers (specificity of 99% for first degree relatives and sensitivity of 65%)[12] and a systematic review of the accuracy of reporting of family history concludes that first degree histories are accurate and valuable for clinical risk assessment.[13] We have previously shown high rates of agreement between self-report data and medical diagnosis in this cohort of women trained as registered nurses [14], suggesting they should perform as well or better than those in population based studies of reporting accuracy. As the data are analyzed prospectively, any recall error should be non-differential.

Incidence of invasive breast cancer in the Nurses' Health Study cohort mirrors SEER incidence rates for white women. For the total cohort before exclusions the observed incidence of breast cancer is comparable to the expected incidence based on the SEER rates [15] for white women, 1988–1992 (O/E = 1.0; 95%CI 0.98–1.03).

A larger cohort for analysis could provide refined measures for US women with intermediate to extensive pedigrees, but the prevalence of such subgroups is low in the general population as noted in this group of women. Family history as defined here for mother or sister can be a useful contributor to clinical risk assessment in general.[13,16]

However, more refined assessments including the extensive assessment of family pedigree has a more limited clinical application with genetic counseling and more intensive options than lifestyle consideration for risk reduction such as bilateral oophorectomy among women with BRCA1 or 2.[17] Recent data assessing SNPs related to breast cancer shows that even with these in analysis family history remains associated with breast cancer risk and there is no meaningful interaction with family history. [18]

Current cancer screening guidelines recommend screening at an earlier age or more frequently for individuals with a family history of multiple cancers, including breast, ovarian, colorectal, prostate and skin (melanoma) cancer. [19–21] The recommendation for routine mammography screening from the US Preventive Services Task Force was strengthened by a family history of breast cancer diagnosed before menopause.[22] Because family history can inform risk for multiple common cancers, this information could be used as the basis for multiple prevention or screening recommendations, including recommendations for breast cancer screening. [23–24] However, collection of family history information is currently a missed prevention opportunity for many. Although 96% of respondents to a national survey conducted in 2004 believed that their family history information is important for their own health, less than 30% had actively collected such information from relatives.[24] Even among those who discuss the information with relatives, only a small percentage record written details about family members' conditions necessary to tailor prevention and screening recommendations.[25] In addition, clinicians in general practice might not collect sufficient family history information to assess cancer risk and tailor screening recommendations.[13,26–27] Initiatives to encourage the collection of family history information among women and discussion of this information with health care providers may be an important strategy to reach those at increased risk of breast cancer.

Studies of family history show a modest decrease in risk with advancing maternal age at diagnosis. Since the relative risk associated with family history represents a multiplication of risk among women with out such a history, the absolute excess risk associated with a positive family history will be greater among women at higher risk for other reasons. Our finding of consistent effects for lifestyle and reproductive factors among those with and without family history adds to a robust framework for risk stratification and counseling for modifications in lifestyle (weight loss after menopause [28], increase in physical activity, reduction in alcohol[29]) that may lower risk even among women with family history.

Conclusion

Based on this extensive follow-up of the Nurses' Health Study with over 1.6 million person years of follow-up we conclude that mother or sister diagnosed with breast cancer before age 50 and at age 50 or later is the best classification for these data and provides clinically useful approach to stratify risk for women. In a general population cohort with breast cancer incidence reflecting national rates, the prevalence of mother and sister positive history of breast cancer is too low to be meaningfully evaluated. In clinical practice, in general, this will also apply. Collection of family history remains important for prevention since this information can impact risk for cancers beyond just breast.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Distribution of Covariates in 1990, by family history and age at first diagnosis among family member, Nurses' Health Study, 1980 through 2006*

Table 1

Variable	No Family history			Family history <50			Family history age 50+		
	mean	sd	N	mean	sd	N	mean	sd	N
Age	55.5	7.6	59088	55.2	7.3	2383	56.6	7.4	8334
Age at menarche	12.5	1.4	59088	12.5	1.4	2383	12.6	1.4	8334
Age at 1 st birth**	25.2	3.4	55534	25.2	3.4	2252	25.3	3.4	7808
Parity	2.9	1.6	59088	3.0	1.7	2383	2.9	1.7	8334
Nulliparous (%)	6.0		59088	5.5		2383	6.3		8334
Current BMI (kg/m ²)	23.9	8.0	59088	24.3	7.3	2383	24.4	7.4	8334
BMI at age 18	21.3	3.0	59088	21.3	3.0	2383	21.3	3.0	8334
Height (in)	64.5	2.4	59088	64.6	2.4	2383	64.5	2.4	8334
Alcohol (g/day)	5.4	10.1	59088	5.0	9.3	2383	5.6	10.3	8334
Age at menopause	48.2	5.1	40327	48.2	5.2	1616	48.5	5.1	6128
Current smoking (%)	18.9			17.1			15.9		
Past smoking (%)	32.3			33.4			34.7		
Benign Br disease(%)	37.0			47.6			45.2		

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Mothers age at diagnosis, sisters age at diagnosis, and relative risk of breast cancer in the Nurses' Health Study, 1980 to 2006

Table 2

		No family history	Age<50	Age 50 or greater	Comparison of MV RRs
		3614 py 1370645 1.0 (reference)			
Mother history	Cases P-Y Age-adj RR MV-RR /		104 py 22532 1.83 (1.50, 2.22) 1.69 (1.39, 2.05)	331 py 82679 1.47 (1.28, 1.60) 1.37 (1.22, 1.53)	P=0.06
Sister history	Cases P-Y Age-adj RR MV-RR /		116 py 23088 1.74 (1.44, 2.10) 1.66 (1.38, 1.99)	167 py 33437 1.57 (1.34, 1.84) 1.52 (1.29, 1.77)	P=0.43
Mother or sister	Cases P-Y Age-adj RR MV-RR /		219 py 44755 1.77 (1.54, 2.03) 1.70 (1.48, 1.95)	467 py 110605 1.45 (1.32, 1.60) 1.40 (1.27, 1.54)	P=0.016

/ Multivariate Relative Risk is adjusted for variables in table 3 (age, duration of premenopause, menopause (type and duration), pregnancy history, benign breast disease, postmenopausal hormone therapy (type, duration and current or past use), body mass index, height, and alcohol use)

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brcmodel.mother.sisterhx.4modela.saslog 1 april 2011

Table 3

Established breast cancer risk factors among women without and with family history of breast cancer, breast cancer incidence model, Nurses' Health Study, 1980–2006

Variable	No family history			Yes Family History		
	Beta	se	p-value	Beta	se	p-value
Intercept	-8.9894	0.1870	<0.001	-7.6201	.5138	<0.001
Duration of premenopause (yrs)	0.0741	.00522	<0.001	0.0480	.0139	0.0005
Menopause, duration						
Natural	0.0184	.00318	<0.001	0.0184	.00739	0.0127
Bilateral oophorectomy	0.0171	.00444	0.001	0.00272	.0102	0.79
Pregnancy history						
Age at 1 st birth - age at menarche	0.00755	.00348	0.03	0.00496	.00824	0.55
Birth index	-0.00360	.000518	<0.001	-0.00215	.00117	0.061
BBD						
BBD (yes vs. no)	0.8013	.3689	0.03	0.2669	.8718	0.76
BBD x Age at menarche	0.0161	.0179	0.37	0.0534	.0381	0.16
BBD x Duration of premenopause	-0.0139	.00687	0.04	-0.0130	.0169	0.44
BBD x Duration of menopause	-0.0143	.00362	<0.001	-0.0133	.00841	0.11
Postmenopause hormone (PMH)						
Duration of oral estrogen use alone (yrs) during postmenopause	0.0183	.00559	0.001	-0.00516	.0130	0.69
Duration of oral estrogen and progesterone (yrs) during postmenopause	0.0347	.00695	<0.001	0.00723	.0154	0.64
Duration of use of other types of postmenopausal hormones	0.00673	.00709	0.34	-0.0115	.0157	0.46
During postmenopause						
Current PMH use	0.2740	.0500	<0.001	0.3838	.1177	0.0011
Past PMH use	-0.2771	.0527	<0.001	-0.1030	.1132	0.36
BMI						
(Average BMI during premenopause - 21.8) x Duration of premenopause ⁺	-0.00101	.000166	<0.001	-0.00066	.000399	0.10
(Average BMI during postmenopause - 24.4) x Duration of postmenopause	0.00286	.000386	<0.001	0.00216	.000837	0.010
Height						

Variable	No family history			Yes Family History		
	Beta	se	p-value	Beta	se	p-value
(Height - 64.5) x Duration of premenopause ⁺	0.000459	.000211	0.03	0.00111	.000522	0.034
(Height - 64.4) x Duration of postmenopause	0.000315	.000852	0.71	-0.00122	.00182	0.50
Alcohol						
Cumulative grams premenopause	.000414	.000093	<0.001	.000341	.000228	0.13
Cumulative grams postmenopause						
While on PMH	-0.00018	.000254	0.49	.00127	.000525	0.016
While not on PMH	.000251	.000187	0.18	-.00010	.000407	0.80
Number of cases	3641			686		
Number of person-years	1,370,645			155,360		

Model results updated for C: brcnmodel.mother.sisterhx.stratify.2models.saslog 8-april-2011