Title

Family history of breast cancer, breast density, and breast cancer risk in a U.S. breast cancer screening population

Running title

Detailed family history, density, and breast cancer risk

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ABSTRACT

Background: The utility of incorporating detailed family history into breast cancer risk prediction hinges on its independent contribution to breast cancer risk. We evaluated associations between detailed family history and breast cancer risk while accounting for breast density.

Methods: We followed 222,019 participants aged 35-74 in the Breast Cancer Surveillance Consortium, of whom 2,456 developed invasive breast cancer. We calculated standardized breast cancer risks within joint strata of breast density and simple (1st-degree female relative) or detailed (1st-degree, 2nd-degree, or 1st- and 2nd-degree female relative) breast cancer family history. We fit log-binomial models to estimate age-specific breast cancer associations for simple and detailed family history, accounting for breast density.

Results: Simple 1st-degree family history was associated with increased breast cancer risk compared with no 1st-degree history (RR=1.5, 95%CI 1.0-2.1 at age 40; RR=1.5, 95%CI 1.3-1.7 at age 50; RR=1.4, 95%CI 1.2-1.6 at age 60; RR=1.3, 95%CI 1.1-1.5 at age 70). Breast cancer associations with detailed family history were strongest for women with 1st- and 2nd-degree family history compared with no history (RR=1.9, 95%CI 1.1-3.2 at age 40); this association weakened in higher age groups (RR=1.2, 95%CI 0.88-1.5 at age 70). Associations did not change substantially when adjusted for breast density.

Conclusion: Even with adjustment for breast density, a history of breast cancer in both 1st- and 2nd-degree relatives is more strongly associated with breast cancer than simple 1st-degree family history.

Impact: Future efforts to improve breast cancer risk prediction models should evaluate detailed family history as a risk factor.

Introduction

Breast cancer risk prediction has steadily evolved since the 1989 publication of the Gail model (1). First-degree family history of breast cancer is one of the original Gail model parameters; it is easy to ascertain, provides information on inherited risk, and has consistently appeared in subsequent predictive models (1-7). Among women with a family history of breast cancer, personal risk fluctuates as a function of the type and number of affected relatives and the ages at which those relatives were diagnosed (8, 9). Despite these nuances, most predictive models characterize family history among 1st-degree female relatives (1, 2, 4-7), though some incorporate the number of such relatives affected or their ages at diagnosis (1, 3-5). The predictive capability of these models might be improved through more detailed assessment of family history, as allowed by the IBIS and BOADICEA models (3, 10).

Some recent breast cancer risk models include mammographic breast density in their set of predictors (4-6). Mammographic measures of breast density assess the relative contribution of dense and non-dense tissue to total breast area. Dense area—comprised of parenchymal and stromal elements—is radiopaque and appears bright on the film; non-dense area—comprised of fat tissue—is radiolucent and appears dark (11). Based on the Breast Imaging Reporting and Data System (BI-RADS) density categories, women with "extremely dense" breasts have roughly 4.1 times greater breast cancer risk compared with women whose breasts are "almost entirely fat" (12). The strong association between density and risk translates into modest predictive capacity; four different risk models, all of which included 1st-degree family history, saw increases of 0.01 to 0.07 in the area under their receiver-operating characteristic curves when mammographic density was added to the vector of predictors (4, 6, 7, 13).

We investigated two questions to inform whether detailed family history should be considered in future predictive risk model development. First, we evaluated whether characterization of family history beyond 1st-degree relatives associates with invasive breast cancer independent of breast density. Evidence from previous studies suggests a positive association between family history and density (14-17), but the nature of this association (e.g., whether causal or the result of shared genetics) is unknown. Second, we evaluated whether

detailed assessment of family history reveals more nuanced associations with breast cancer risk compared with simple assessment of family history.

Materials and Methods

Source population

We conducted this cohort study within the Breast Cancer Surveillance Consortium (BCSC), a network of mammography registries whose participants provide a representative sample of U.S. women undergoing screening mammography (18). We included subjects from BCSC registries which collected data on extended family history. These registries covered the San Francisco Bay Area, Western Washington (specifically, enrollees in the Group Health Cooperative health system), and the state of Vermont. Women age 35-74 years entered the study at the time they underwent a screening mammogram between 1996 and 2013. Women could contribute multiple mammograms and subsequent years of follow-up to the study. Observations under this design have been shown to be statistically independent, assuming that the probability of incident cancer diagnosis with 12 months of mammography (conditional on covariates measured at that examination) does not depend on the observation number in the analysis or on covariates measured at other mammography visits (19). Women were excluded if they had a personal history of invasive breast cancer or *in situ* disease, prophylactic mastectomy, or if they had breast implants. We also excluded women if breast density information was unavailable, or if both first- and second-degree family history of breast cancer were not ascertained at the time of mammography. Each registry obtains annual Institutional Review Board approval for consenting processes (or a waiver of consent), enrollment of participants, and data linkages for research purposes. All registries received a Federal Certificate of Confidentiality that protects the identities of research participants.

Definitions of analytic variables

Family history of breast cancer was ascertained with self-administered questionnaires completed at the time of mammography. Subjects were asked to consider only blood relatives and to report whether a mother, sister, daughter, grandmother, aunt, or male relative had been diagnosed with breast cancer. Simple family history was positive if at least one 1st-degree female relative (mother, sister, or daughter) had been diagnosed with breast cancer before the subject's mammogram date, and was otherwise deemed negative. Under the

simple definition, women with a positive first-degree history could have more than one affected 1st-degree relative and/or have affected 2nd-degree relatives. Furthermore, women with a negative 1st-degree history may have had affected 2nd-degree relatives. For detailed family history, we defined mutually exclusive categories of no family history, history only in ≥1 2nd-degree female relative (grandmother or aunt), history only in ≥1 1st-degree female relative, history in ≥1 1st-degree female relative and ≥1 2nd-degree female relative, and history in a male relative (regardless of female relative family history). Under the detailed family history definition, women with a negative family history had no 1st- or 2nd-degree female or male relative. Therefore, the reference groups were not identical for the simple and detailed definitions of family history.

Breast density was defined using the BI-RADS categories. Under this system, a woman's breast density is qualitatively assigned to one of four ordinal categories following evaluation of bilateral breast images by a radiologist: a=almost entirely fat, b=scattered fibroglandular densities, c=heterogeneously dense, and d=extremely dense (20, 21)

Cases of incident invasive breast cancer were ascertained by each BCSC registry through linkage with their regional Surveillance, Epidemiology, and End Results (SEER) programs, state cancer registries, and with local pathology databases. Women were followed for 12 months after their screening mammogram for breast cancer diagnosis.

Age at the time of mammogram was categorized in 5-year groups for tabular presentation (beginning with age 35 and ending at age 74), but was modeled in continuous form with linear and quadratic terms. Body mass index (kg/m^2) was categorized as <18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, ≥35.0, or missing, but was modeled in continuous form with linear and quadratic terms. Age at first birth was categorized as nulliparous, age <30, age ≥30, or missing. Age at menopause was categorized as premenopausal, <40, 40-49, 50-54, ≥55, or missing. Current use of postmenopausal hormone therapy and family history of ovarian cancer were both classified dichotomously.

Statistical analysis

We tabulated the frequency and proportion of subjects' characteristics within detailed family history categories, including the frequency of missing observations. We used predictive margins (22) to estimate age-

and BMI-standardized one-year cumulative incidence of breast cancer as a joint function of family history (simple or detailed) and BI-RADS breast density. We estimated 95% confidence limits for the standardized risk estimates by applying Taylor approximations to logit-transformed incidence proportions (22). We fit multivariable log-binomial models to estimate associations between simple or detailed family history and one-year breast cancer incidence. Independent variables in these models included either simple or detailed family history, age and age squared (centered at age 50), BMI and BMI squared (centered at the mean BMI of 27.54), race/ethnicity, and BCSC registry. We fit these same models with further adjustment for BI-RADS breast density. Family history and body mass index were allowed to vary with each observation. We report modeled risk ratios associating family history with breast cancer incidence (with and without adjustment for breast density) for ages 40, 50, 60, and 70.

By design, all subjects had non-missing family history and breast density. Subjects with missing values for specific variables were excluded from any analysis using those variables. Analyses were carried out with R statistical software, version 3.2.2.

Results

Table 1 shows characteristics of the 222,019 members of the cohort according to detailed family history category. There were missing observations for BMI (6.4%), age at first birth (2.4%), age at menopause (13%), use of postmenopausal hormones (3.5%), race/ethnicity (0.7%), and family history of ovarian cancer (24%). Most women (65%) had no family history of breast cancer, 18% had only a 2nd-degree family history, 11% had only a 1st-degree family history, 5.1% had both 1st- and 2nd-degree family history, and only 0.6% had a family history in a male relative. Distributions of age at mammogram, BMI, BI-RADS density, age at first birth, age at menopause, and postmenopausal hormone use were similar across family history categories (Table 1). Eighty-two percent of Asian women had no family history of breast cancer, compared with 61-73% of women from other race/ethnicity groups (Supplemental Table 1). Family history of ovarian cancer was positively associated with breast cancer family history (8.9% of women with an ovarian cancer family history had history of breast cancer in both 1st- and 2nd-degree relatives, compared with 4.9% of women without an ovarian cancer family history; Supplemental Table 1).

Table 2 reports age- and BMI-standardized estimates of one-year breast cancer risk according to simple or detailed family history and BI-RADS breast density. Breast cancer risk increased monotonically with breast density in simple family history groups, and absolute risks were consistently higher for women with at least one 1st-degree relative than for women without a 1st-degree relative (Table 2). Among women without a 1st-degree history, risk increased from 1.4 cases per 1,000 women in the "almost entirely fat" density group to 5.8 cases per 1,000 women in the "extremely dense" group. By comparison, among women with a first-degree family history, risk increased from 2.1 cases per 1,000 women in the "almost entirely fat" group to 8.7 cases per 1,000 women in the "extremely dense" group. Breast cancer risk also increased as a function of BI-RADS density in all categories of the detailed family history classification. The most marked trend in risk elevation was seen in women with family history in a male relative, among whom risk increased from 2.2 cases per 1,000 women in the "almost entirely fat" group to 10.9 cases per 1,000 women in the "extremely dense" group. This was similar to the risk trend among women with only a 1st-degree family history, ranged from 1.8 to 10.0 cases per 1,000 women in the lowest and highest BI-RADS groups, respectively. Women with both first- and second-degree history had the highest absolute risk in the lowest BI-RADS density group (2.6 cases per 1,000 women), which increased as a function of density to 6.8 cases per 1,000 women in the highest density group.

Table 3 shows modeled risk ratios associating simple or detailed family history with incident breast cancer for women by decade of age. Without adjusting associations for BI-RADS density, both simple and detailed family history in female relatives were positively associated with breast cancer. Simple 1st-degree family history was associated with an increased breast cancer risk compared with no 1st-degree history (Risk ratio(RR)=1.5, 95%CI 1.0-2.1 at age 40; RR=1.5, 95%CI 1.3-1.7 at age 50; RR=1.4, 95%CI 1.2-1.6 at age 60; RR=1.3, 95%CI 1.1-1.5 at age 70). The decrease in association strength with age was also seen for detailed family history categories (Table 3), with only weak or null associations seen in the age 70 stratum (e.g., for 1st- and 2nd-degree history, RR=1.2, 95%CI 0.88-1.5). In the younger age strata, family history in both 1st- and 2nd-degree female relatives was more strongly associated with breast cancer than simple first-degree family history. For example, in the age 40 stratum, history in both 1st- and 2nd-degree female relatives was associated with a 90% increase in breast cancer risk (95%CI 10%-220%), whereas simple first-degree family history was associated with a 50% increase in breast cancer risk (95%CI 0%-110%). Associations between male relative

family history and breast cancer were non-significant, though imprecisely estimated, in all strata. Family history associations did not change substantially when adjusted for BI-RADS density.

Discussion

We evaluated whether mammographic breast density and family history of breast cancer were independently associated with breast cancer risk, and whether a more detailed classification of family history revealed associations that were not evident with a simple classification. We observed that BI-RADS breast density was positively associated with breast cancer risk in all levels of detailed family history, and that absolute risks increased with more extensive family history in all BI-RADS density strata (Table 2). Multivariable analyses showed that history in both 1st- and 2nd-degree female relatives was more strongly associated with breast cancer than simple 1st-degree family history among younger women, and that all family history associations were robust to adjustment for breast density. Taken together, these results suggest that incorporating a more detailed assessment of breast cancer family history into risk models may improve predictive power even when breast density is included in the model.

Breast cancer cumulative incidence estimates differed between the reference groups for the simple and detailed definitions of family history ("no 1st-degree history" and "no family history", respectively; Table 2). This is likely because the composition of the two reference groups differed; the simple definition classified women with affected 2nd-degree and male relatives into the reference group, while the detailed definition classified such women into distinct index categories. The proportion of women with affected 2nd-degree relatives in the simple definition reference category may not have been constant across BI-RADS categories, which would explain why cumulative incidences were not uniformly higher under the simple definition, compared with the detailed definition.

Other studies have evaluated relationships between breast density, family history, and breast cancer incidence. Maskarinec *et al* showed that the association between breast density and incident breast cancer was stronger among women with a 1st-degree family history compared with women without family history (16). This was also evident from our standardized risks (Table 2) under our detailed classification of family history (i.e., there was an approximately 5.5-fold increase in risk when comparing the extremely dense BI-RADS group

with the almost entirely fat BI-RADS group among women with only a first-degree family history, and a 3.9-fold increase in risk when comparing the extremely dense BI-RADS group with the almost entirely fat BI-RADS group among women without a family history). Although this was not evident under our simple classification of family history, a study by Yaghjyan *et al.* did not observe modification of the density/breast cancer association by first-degree family history (23). In a source population overlapping ours, Ziv *et al* showed that women in higher BI-RADS categories had higher odds of a first-degree family history than women in the lowest BI-RADS category (17). Martin *et al.* noted that breast density increased as a function of the number of 1st-degree relatives affected with breast cancer in an independent study population (15) and Crest *et al.,* also in an overlapping population, observed the same association when assessing the number of both first- and second-degree relatives affected (14). We did not see a corresponding pattern between BI-RADS density and our detailed family history categorization (Table 1). Martin *et al.* further showed that associations between breast density and breast cancer risk strengthened as the number of affected first-degree relatives increased (15). While we could not assess the number of affected first-degree relatives (because not all participating registries collected that information), we did see that having both a first- and second-degree family history was more strongly associated with breast cancer incidence than having only a 1st-degree history or only a 2nd-degree history (the latter two definitions having fewer relatives, on average, than the former definition; Table 3).

The prevalence of first-degree history in our cohort (approximately 16%) was about 4% higher than that among women aged 40—74 in the U.S. National Health Information Survey (NHIS) [unpublished data; see (24) for age group-specific prevalence estimates for all NHIS respondents]. A slightly higher prevalence of family history in our cohort is expected, since women with a family history are more likely to undergo regular screening. Regardless, slight deviations from a general population sample should not impact the suitability of the BCSC cohort to address questions about risk prediction involving measures of breast density; indeed the cohort is closely tailored to the population of women who stand to benefit from refinement of those tools. Our study's chief limitations are potential misclassification of family history, use of the qualitative BI-RADS system for classifying breast density, and low numbers of subjects with breast cancer history in male relatives. We note that limitations with respect to misclassification of family history by self-report and of breast density by the BI-RADS system may be moot, as these imperfect measurements are quite often the only basis available for

breast cancer risk prediction in clinical practice nationwide. Studies validating self-reported breast cancer family history against relatives' medical records showed excellent classification of 1st-degree history (across 4 studies the range of sensitivities was 85-98% and the range of specificities was 96-99%), but less reliable classification of second-degree history (one study; sensitivity=82 and specificity=91) (25). Misclassification of detailed family history could therefore bias our reported associations, and while errors are likely to be non-differential, the direction of bias is unpredictable since the exposure is polytomous (26). As with other studies that assess 1st-degree family history, our simple definition of family history relied on a reference group (i.e., women with no first-degree family history of breast cancer in a female relative), which likely contains women with 2nd-degree relatives and male relatives affected by breast cancer. In this case, a bias of effect measures toward the null can be reasonably expected. Despite this possibility, the modeled risks in Table 2 were similar between the simple and detailed definitions' reference groups (the latter of which is expected to be purer in terms of absence of family history), so the bias is likely negligible. Our results pertaining to family history in male relatives are based on very small numbers of exposed subjects, and should be taken as only exploratory findings.

Though widely used, the qualitative BI-RADS breast density classification system was not originally intended to quantify breast density for the purpose of estimating breast cancer risk. Rather, it serves to inform referring physicians about the likelihood of lesion masking by dense tissue (27). Our study relied on BI-RADS measurements reported by radiologists at many radiology facilities within BCSC registries. Inter-observer agreement on BI-RADS categories is modest, particularly for the two intermediate levels (28). Nonetheless, the contrast between the lowest and highest BI-RADS categories should be relatively robust to inter-observer variation. Furthermore, clinical BI-RADS density and commercially available automated measures of breast density show similar, strong associations with breast cancer (29).

We followed women for incident breast cancer within one year of mammography. While this is a short duration of follow-up, it is expected to capture breast cancer cases regardless of mode of detection and to yield risk factor associations comparable with those observed in studies with longer follow-up (4).

In addition to its large size and prospective design, our study has a number of strengths. The BCSC population is highly representative of the U.S. women who undergo breast cancer screening, and breast cancer follow-up was complete for all subjects. We were also able to characterize family history beyond first-degree female relatives, and account for the confounding influence of several key factors such as age, adiposity, and race/ethnicity.

In summary, detailed classification of breast cancer family history showed associations with incident breast cancer beyond those seen with the simpler, more typical, assessment of 1st-degree history. Furthermore, these associations were robust to adjustment for breast density. Together, these findings support the development of breast cancer risk prediction models that include both breast density and 1st- and 2nd-degree measures of breast cancer family history—especially in prediction of risk for younger women. Opportunities for future studies on this topic include the evaluation of the number of affected relatives (and their ages at diagnosis) within the expanded categories of family history, and focusing on the contribution of affected male relatives to individual risk.

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The National Cancer Institute had no role in the study's design; the collection, analysis, and interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication.

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Table 1

Characteristics of the study population (one random observation per woman, n=222,019) according to family history. Frequency and column percentage.

Characteristic	No family history n=144,930 (65%)		2nd degree only n=40,253 (18%)		1st degree only n=24,028 (11%)		1st and 2nd degree n=11,376 (5.1%)		Male relative * n=1,432 (0.6%)	
Age group, years, n (%)										
35-39	7,100	(4.9)	3,270	(8.1)	1,313	(5.5)	931	(8.2)	79	(5.5)
40-44	22,043	(15)	8,118	(20)	2,835	(12)	1,670	(15)	193	(14)
45-49	24,738	(17)	7,654	(19)	3,536	(15)	1,878	(17)	265	(19)
50-54	26,259	(18)	7,060	(18)	3,933	(16)	2,006	(18)	233	(16)
55-59	22,714	(16)	5,478	(14)	3,970	(17)	1,788	(16)	241	(17)
60-64	18,603	(13)	4,212	(11)	3,572	(15)	1,444	(13)	173	(12)
65-69	13,022	(9.0)	2,769	(6.9)	2,645	(11)	973	(8.6)	147	(10)
70-74	10,451	(7.2)	1,692	(4.2)	2,224	(9.3)	686	(6.0)	101	(7.1)
Body mass index, n (%)										
BMI < 18.5	2,528	(1.9)	559	(1.5)	415	(1.8)	162	(1.5)	24	(1.9)
18.5 ≤ BMI < 24.9	54,876	(41)	14,968	(39)	9,032	(40)	4,162	(38)	471	(36)
25.0 ≤ BMI < 29.9	40,591	(30)	11,154	(29)	6,813	(30)	3,265	(30)	404	(31)
30.0 ≤ BMI < 34.9	20,240	(15)	6,175	(16)	3,437	(15)	1,740	(16)	216	(17)

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BMI ≥ 35.0	16,591	(12)	5,569	(15)	2,753	(12)	1,586	(15)	179	(14)
[Missing]	10,104		1,828		1,578		461		138	
BI-RADS breast density, n (%)										
Almost entirely fat	14,147	(9.8)	3,339	(8.3)	2,193	(9.1)	908	(8.0)	149	(10)
Scattered fibroglandular densities	52,532	(36)	13,960	(35)	8,766	(37)	3,987	(35)	511	(36)
Heterogeneously dense	60,666	(42)	17,724	(44)	10,157	(42)	5,008	(44)	616	(43)
Extremely dense	17,585	(12)	5,230	(13)	2,912	(12)	1,473	(13)	156	(11)
Age at first birth, n (%)										
Nulliparous	34,640	(25)	10,240	(26)	5,965	(26)	2,848	(26)	358	(26)
Age < 30	77,148	(55)	20,363	(52)	12,772	(55)	6,029	(54)	762	(55)
Age ≥ 30	29,552	(21)	8,702	(22)	4,682	(20)	2,278	(20)	264	(19)
[Missing]	3,590		948		609		221		48	

Characteristic	No family history n=144,930 (65%)		2nd degree only n=40,253 (18%)		1st degree only n=24,028 (11%)		1st and 2nd degree n=11,376 (5.1%)		Male relative * n=1,432 (0.6%)	
Age at menopause, years, n (%)										
Premenopausal	44,836	(36)	15,616	(44)	6,575	(32)	3,660	(36)	390	(32)
< 40	10,407	(8.2)	3,328	(9.3)	1,831	(8.8)	1,158	(12)	138	(11)
40—49	30,846	(24)	7,376	(21)	5,026	(24)	2,311	(23)	323	(26)
50—54	32,125	(25)	7,407	(21)	5,775	(28)	2,361	(23)	305	(25)
≥ 55	8,257	(6.5)	1,950	(5.5)	1,598	(7.7)	598	(5.9)	71	(5.8)
[Missing]	18,459		4,576		3,223		1,288		205	
Postmenopausal hormones, n (%)										
Yes	21,590	(15)	6,187	(16)	3,304	(14)	1,632	(15)	168	(12)
No	117,952	(85)	32,778	(84)	19,789	(86)	9,388	(85)	1,193	(88)
[Missing]	5,388		1,288		935		356		71	

Characteristic	No family history n=144,930 (65%)		2nd degree only n=40,253 (18%)		1st degree only n=24,028 (11%)		1st and 2nd degree n=11,376 (5.1%)		Male relative * n=1,432 (0.6%)	
Race/ethnicity, n(%)										
White, non-Hispanic	94,056	(65)	32,844	(82)	17,893	(75)	9,479	(84)	912	(64)
Black, non-Hispanic	6,009	(4.2)	1,341	(3.3)	990	(4.1)	381	(3.4)	89	(6.3)
Asian	29,129	(20)	2,591	(6.5)	3,025	(13)	580	(5.1)	223	(16)
American Indian/ Alaska Native	567	(0.4)	153	(0.4)	110	(0.5)	45	(0.4)	8	(0.6)
Hispanic	9,662	(6.7)	1,781	(4.4)	1,173	(4.9)	444	(3.9)	135	(9.5)
Other	4,411	(3.1)	1,328	(3.3)	684	(2.9)	398	(3.5)	57	(4.0)
[Missing]	1,096		215		153		49		8	
Ovarian cancer in family, n (%)										
Yes	6,026	(5.4)	2,393	(8.1)	1,608	(8.9)	999	(12)	174	(15)
No	106,024	(95)	27,239	(92)	16,411	(91)	7,696	(89)	980	(85)
[Missing]	32,880		10,621		6,009		2,681		278	

Proportions may not add to 100% due to rounding. * Women with a male relative affected by breast cancer were placed in the male relative category regardless of breast cancer among female relatives.

Table 2

Standardized cumulative incidence of invasive breast cancer (cases per thousand women at risk) in joint strata of BI-RADS breast density and simple or detailed family history among Breast Cancer Screening Consortium participants, 1996-2013.

Family history		Cases	Almost entirely fat (n=20,736)	Scattered fibroglandular densities (n=79,756)	Heterogeneously dense (n=94,171)	Extremely dense (n=27,356)
Simple	No first-degree history	1,789	1.4 (1.4, 1.5)	3.4 (3.2, 3.5)	5.2 (5.0, 5.5)	5.8 (5.5, 6.1)
	First-degree family history	667	2.1 (2.0, 2.2)	4.7 (4.5, 4.9)	7.8 (7.4, 8.2)	8.7 (8.1, 9.3)
Detailed	No family history	1,329	1.5 (1.5, 1.6)	3.3 (3.1, 3.4)	5.0 (4.8, 5.2)	5.8 (5.5, 6.1)
	Second degree only	452	1.0 (0.9, 1.0)	3.6 (3.4, 3.8)	5.9 (5.6, 6.2)	5.8 (5.4, 6.1)
	First degree only	424	1.8 (1.8, 1.9)	4.4 (4.2, 4.6)	8.0 (7.7, 8.4)	10.0 (9.3, 10.8)
	First and second degree	232	2.6 (2.5, 2.7)	5.2 (4.9, 5.4)	7.3 (7.0, 7.6)	6.8 (6.3, 7.2)
	Male *	19	2.2 (2.1, 2.3)	5.4 (5.1, 5.6)	5.8 (5.6, 6.1)	10.9 (10.4, 11.4)

Standardized using predictive marginals based on breast density (categorical), family history (categorical), age (continuous), age^2 (continuous), BMI (continuous), and BMI^2 (continuous), with interactions between breast density and family history, age, age squared, body mass index, and body mass index squared, and with interactions between family history and age, age squared, body mass index, and body mass index squared. Confidence intervals estimated using Delta method approximations of the standard error.

* Women with a male relative affected by breast cancer were placed in the male relative category regardless of breast cancer among female relatives.

Table 3

Associations between simple or detailed breast cancer family history and incident invasive breast cancer, with and without adjustment for mammographic breast density.

Stratum	Family history		Cases/ total	Risk ratio (95% confidence interval)			
				Multivariable, without density [1]		Multivariable, with density [2]	
Age 40	Simple	No first-degree history	123/ 74,024	1.0	Ref	1.0	Ref
		First-degree family history	41/ 14,692	1.5	(1.0, 2.1)	1.5	(1.0, 2.1)
	Detailed	No family history	78/ 51,275	1.	Ref	1.	Ref
		Second degree only	45/ 22,446	1.3	(0.84, 1.9)	1.3	(0.84, 1.9)
		First degree only	20/ 8,774	1.4	(0.85, 2.2)	1.4	(0.84, 2.2)
		First and second degree	20/ 5,742	1.9	(1.1, 3.2)	1.9	(1.1, 3.2)
		Male relative	1/ 479	0.91	(0.09, 9.5)	0.90	(0.09, 9.4)
Age 50	Simple	No first-degree history	523/ 158,558	1.	Ref	1.	Ref
		First-degree family history	181/ 34,422	1.5	(1.3, 1.7)	1.5	(1.3, 1.7)
	Detailed	No family history	362/ 116,866	1.	Ref	1.	Ref
		Second degree only	160/ 41,028	1.2	(1.0, 1.4)	1.2	(1.0, 1.4)
		First degree only	110/ 21,165	1.5	(1.2, 1.8)	1.5	(1.2, 1.7)
		First and second degree	69/ 12,824	1.7	(1.3, 2.1)	1.6	(1.3, 2.0)
		Male relative	3/ 1,097	1.4	(0.58, 3.2)	1.4	(0.58, 3.2)

Stratum	Family history		Cases/ total	Risk ratio (95% confidence interval)			
				Multivariable, without density [1]		Multivariable, with density [2]	
Age 60	Simple	No first-degree history	659/ 137,524	1.	Ref	1.	Ref
		First-degree family history	254/ 35,946	1.4	(1.2, 1.6)	1.4	(1.2, 1.6)
	Detailed	No family history	493/ 105,487	1.	Ref	1.	Ref
		Second degree only	161/ 31,385	1.1	(0.93, 1.3)	1.1	(0.91, 1.3)
		First degree only	160/ 23,008	1.4	(1.2, 1.7)	1.4	(1.2, 1.7)
		First and second degree	91/ 12,488	1.4	(1.2, 1.7)	1.4	(1.1, 1.7)
		Male relative	8/ 1,102	1.7	(0.84, 3.4)	1.7	(0.82, 3.3)
Age 70	Simple	No first-degree history	484/ 70,704	1.	Ref	1.	Ref
		First-degree family history	191/ 20,485	1.3	(1.1, 1.5)	1.2	(1.1, 1.5)
	Detailed	No family history	396/ 56,752	1.	Ref	1.	Ref
		Second degree only	86/ 13,554	0.95	(0.76, 1.2)	0.93	(0.75, 1.2)
		First degree only	134/ 14,095	1.3	(1.05, 1.5)	1.3	(1.0, 1.5)
		First and second degree	52/ 6,087	1.2	(0.88, 1.5)	1.1	(0.85, 1.5)
		Male relative	7/ 701	1.7	(0.80, 3.4)	1.6	(0.78, 3.3)

[1] Adjusted for age, age squared, body mass index, body mass index squared, race/ethnicity, and registry.

[2] Adjusted for age, age squared, body mass index, body mass index squared, race/ethnicity, registry, and BI-RADS density category.

* Women with a male relative affected by breast cancer were placed in the male relative category regardless of breast cancer among female relatives.

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