Published in final edited form as:

Breast Cancer Res Treat. 2011 April ; 126(3): 671–678. doi:10.1007/s10549-010-1148-9.

Family History of Breast Cancer in First-Degree Relatives and Triple-Negative Breast Cancer Risk

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Abstract

Purpose—Triple-negative breast cancer accounts for less than 20% of breast cancers overall, but is the predominant subtype among carriers of mutations in *BRCA1*. However, few studies have assessed the association between breast cancer family history and risk of triple-negative breast cancer. We examined the relationship between having a family history of breast cancer in first-degree relatives and risk of triple-negative breast cancer, and risk of two other breast cancer subtypes defined by tumor marker expression.

Methods—We evaluated data collected by the Breast Cancer Surveillance Consortium from 2,599,946 mammograms on 1,054,466 women, among whom 15% reported a first-degree family history of breast cancer. Using Cox regression in this cohort we evaluated subtype-specific associations between family history and risk of triple-negative (N=705), estrogen receptor-positive (ER+, N=10,026), and hormone receptor-negative / HER2-expressing (ER-/PR-/HER2+, N=308) breast cancer among women aged 40-84 years.

Results—First-degree family history was similarly and significantly associated with an increased risk of all subtypes [hazard ratio (HR)=1.73, 95% confidence interval (CI): 1.43-2.09, HR=1.62, 95% CI: 1.54-1.70, and HR=1.56, 95% CI: 1.15-2.13, for triple-negative, ER+, and ER-/PR-/HER2+, respectively]. Risk of all subtypes was most pronounced among women with at least two affected first-degree relatives (versus women with no affected first-degree relatives, HR_{triple-negative}=2.66, 95% CI: 1.66-4.27, HR_{ER+}=2.05, 95% CI: 1.79-2.36, HR_{ER-/PR-/HER2+}=2.25, 95% CI: 0.99-5.08).

Conclusions—Having a first-degree family history of breast cancer was associated with an increased risk of triple-negative breast cancer with a magnitude of association similar to that for the predominant ER+ subtype and ER-/PR-/HER2+ breast cancer.

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Conflict of interest: The authors declare that they have no competing interests.

Keywords

family history; breast cancer; triple-negative; estrogen receptor; progesterone receptor; HER2

INTRODUCTION

Mounting evidence indicates that breast cancer is a clinically, biologically, and epidemiologically heterogeneous disease. One subtype of breast cancer that has emerged as being of particular interest in this regard is triple-negative breast cancer. Breast cancers of the triple-negative subtype are characterized by a lack of expression of the estrogen receptor (ER), progesterone receptor (PR), and HER2, and typically exhibit a basal-like pattern of gene expression [1]. Compared to ER-positive (ER+) breast cancers, triple-negative tumors are associated with a poorer survival and more aggressive pathology [2-5]. Although few risk factors for this breast cancer subtype have been identified, a number of studies have reported that triple-negative breast cancer is the predominant subtype among women carrying a deleterious germ-line mutation in *BRCA1*: approximately 57-80% of *BRCA1*-associated breast cancers exhibit the triple-negative phenotype, compared to less than 20% of sporadic breast cancers [6,7]. However, the extent to which the association between *BRCA1* and the triple-negative subtype translates to breast cancer subtype-specific differences in the association with family history of breast cancer has not been well studied.

Given that triple-negative subtype accounts for less than 20% of invasive breast cancers [8,9], and given the relatively recent advent of widespread testing for HER2 expression, few large population-based studies have been able to assess the association between a woman's family history and risk of developing triple-negative breast cancer. Two prior studies evaluated the association between family history and risk of basal-like breast cancer (i.e., triple-negative and positive for EGFR and/or cytokeratin 5/6 expression) [10,11]: one study found no difference in the prevalence of family history among women with basal-like breast cancer as compared to women with ER+ and/or HER2-expressing breast cancers [11], while the other reported an increased breast cancer risk among women with a breast cancer family history that was greatest in magnitude for basal-like breast cancer [10]. In the context of such limited and inconsistent data, the relationship between breast cancer family history and triple-negative breast cancer risk remains unclear.

Using data from the Breast Cancer Surveillance Consortium (BCSC), we assessed the association between family history of breast cancer in first-degree relatives and risk of three breast cancer subtypes defined by ER, PR, and HER2 status among women aged 40-84 years undergoing breast cancer screening.

MATERIALS AND METHODS

The BCSC is a collaborative effort between seven geographically dispersed mammography registries, the details of which have been provided elsewhere [12]. The present analysis includes data from six BCSC registries that collected data on ER, PR, and HER2 status. All BCSC registries collect risk factor information through self-administered questionnaires completed by women at the time of screening mammography [13], including data on attained age, race, Hispanic ethnicity, history of prior breast procedures, and history of breast cancer in first-degree relatives. Women are asked to self-report separately whether breast cancer has previously been diagnosed in: 1) their mother, 2) any sisters, and/or 3) any daughters. Since women may have multiple affected sisters and/or daughters, some BCSC registries also collect information on the number of affected sisters and daughters. All

registries collect some information regarding the age at breast cancer diagnosis of first-degree relatives.

Each registry and the BCSC Statistical Coordinating Center have received institutional review board approval for either active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analytic studies. All procedures are Health Insurance Portability and Accountability Act compliant, and all registries and the Statistical Coordinating Center have received a Federal Certificate of Confidentiality and other protection for the identities of women, physicians, and facilities who are subjects of this research.

Study Population

We included women aged 40-84 years with no prior history of invasive or *in situ* breast cancer at the time of mammography screening. Women meeting these criteria who received at least one screening mammogram [14] at a BCSC-associated facility during the study period were included. The timing and duration of the study period varied between registries, reflecting differences in the earliest breast cancer diagnosis date for which HER2 data were available and the date up to which cancer ascertainment was complete. Registry-specific study period start dates ranged from January 1, 1999 to January 1, 2003; registry-specific study period end dates ranged from May 31, 2007 to October 31, 2008.

After excluding women not meeting eligibility criteria, 2,599,946 mammograms from 1,054,466 women were eligible for inclusion in the present analysis. The average duration of follow-up contributed by women was 3.7 years (range 0-9.0 years) from the time of the first eligible screening mammogram in the study period until either the end of the study period or breast cancer diagnosis, whichever came first. Among the 629,973 women (60%) who received more than one mammogram during the study period, the average time between examinations was 1.5 years (range 0.7-8.9 years).

Case Population

Breast cancers were identified by each BCSC registry through linkage with cancer registries and/or pathology databases. Data on tumor characteristics was also obtained through linkage with these resources. Study cases included women diagnosed with an invasive breast cancer subsequent to a screening mammogram within the study period. The median time between breast cancer diagnosis and a case's most recent prior screening mammogram was 56 days (range 0 days to 8.3 years). Women diagnosed with invasive breast cancer on the same day as their first screening mammogram during the study period (N=431) were recoded such that they contributed one day of follow-up and could thus contribute to the analysis. Women diagnosed with *in situ* breast cancer during the study period (N=3,689) were not considered as cases and were censored at the time of *in situ* diagnosis.

Cases with a HER2 result of 0, 1+, or 2+ on immunohistochemistry (IHC) testing and/or a negative or borderline result on fluorescence *in situ* hybridization (FISH) testing were considered HER2-negative; conversely, cases with positive FISH and/or a HER2 result of 3+ on IHC were considered HER2-expressing. Among 13,797 women diagnosed with invasive breast cancer during the study period, 10,026 were identified as ER+ (regardless of PR and HER2 status), 308 were identified as hormone receptor-negative HER2-expressing (i.e., ER-/PR-/HER2+), and 705 were identified as triple-negative (i.e., ER-, PR-, HER2-). An additional 2,585 cases could not be classified into a subtype due to insufficient tumor marker data (1,562 missing ER status and 1,023 ER-/PR- with missing HER2 status), and 173 were ER- and either PR+ or missing PR status; these cases were censored from all analyses at the time of diagnosis.

Statistical Analyses

We used Cox proportional hazards regression to evaluate the association between history of breast cancer in first-degree relatives and breast cancer risk. Given our interest in assessing risk factor associations separately for different subtypes of breast cancer, we constructed separate regression models specific to each of three breast cancer subtypes of interest (i.e., ER+, ER-/PR-/HER2+, and triple-negative). In all models, the time axis was defined as the time (in days) since a woman's first eligible screening mammogram during the study period, and women diagnosed with invasive breast cancer of a subtype other than the model-specific outcome were censored at the time of diagnosis.

Analyses were adjusted for a limited set of confounders that altered coefficient estimates by at least 10%, including age at the start follow-up (five-year categories), race (white / non-white), and prior history of a benign breast procedure (yes / no). We analyzed the primary exposure of interest, history of breast cancer in first-degree relatives, as a dichotomous variable (yes / no). Exposure variables and covariates other than age were analyzed as time-varying to allow for changes in variable values with mammograms subsequent to the first qualifying mammogram. We evaluated proportional hazards assumptions by testing for a non-zero slope of the scaled Schoenfeld residuals on ranked failure times and on the log of analysis time. Analyses were conducted using STATA SE version 10.1 (College Station, Texas).

In light of previous reports indicating that family history is most strongly associated with breast cancer risk in young women [15,16], we evaluated subtype-specific hazard ratios both overall and within two broad age strata (age 40-54 / 55-84 years). In separate analyses, we examined how subtype-specific associations with family history differed according to the number of affected first-degree relatives and according to the age at which affected relatives were diagnosed with breast cancer. Since two BCSC registries ascertain only whether the participant has an affected sister and/or daughter but not the number of affected sisters or daughters, there were instances where we could not determine whether women reporting a family history had only one or more than one affected first-degree relative. To accommodate this issue, we analyzed the number of affected first-degree relatives as a three-level categorical term: no family history, one or more affected relatives, two or more affected relatives. Although the latter two of these categories overlap, categories were coded to be mutually exclusive; that is, women were included in the middle category only if they reported having one affected relative or if it was not possible to distinguish whether they had only one or more than one affected relatives. The age at breast cancer diagnosis of first-degree relatives was also analyzed as a categorical variable (no family history / family history with no relatives diagnosed before age 50 / family history with one or more relatives diagnosed before age 50). We also compared hazard ratio (HR) estimates across case groups using competing risks partial likelihood methods [17].

Family history variables and most covariates in the regression models were associated with some missingness. Since the exposures and covariates considered here were unlikely to change with great frequency over follow-up, a filling process was used to resolve missing values: missing values of a variable were replaced with non-missing data from the same woman provided at a prior mammogram or, if no prior non-missing data were available, with non-missing data provided at a subsequent mammogram from the same woman. In sensitivity analyses, we also used multiple imputation [18] to assess the impact of missingness in exposures and covariates remaining after filling and the impact of missingness in tumor marker data. Specifically, we constructed an imputation model that included all exposures and covariates, an observation-level categorical outcome indicator variable, the log of analysis time, and tumor characteristics, and applied this imputation model to all analyses.

RESULTS

The distributions of demographic characteristics and covariate variables in the overall study population are presented in Table 1. The majority of the study population was non-Hispanic white (74%) and had education beyond high school (66%). Differences were noted across case groups in the distribution of age at most recent screening mammogram, histologic subtype, and stage and grade at diagnosis (Table 2). In particular, ER+ breast cancers were more likely to be diagnosed as stage I disease (60% versus 40% and 44% in ER-/PR-/HER2+ and triple-negative cases, respectively) and less likely to be classified as high grade (20% in grades 3 and 4 versus 65% and 72% of ER-/PR-/HER2+ and triple-negative cases, respectively).

Women who reported having a family history of breast cancer in first-degree relatives experienced an increased risk of breast cancer that was statistically significant and similar in magnitude with respect to ER+ [HR=1.62, 95% confidence interval (CI): 1.54-1.70], ER-/PR-/HER2+ (HR=1.56, 95% CI: 1.15-2.13), and triple-negative (HR=1.73, 95% CI: 1.43-2.09) subtypes (Table 3). Differences between subtypes were more apparent when analyses were stratified by attained age. HR's characterizing the association between family history and risk of triple-negative breast cancer were almost identical among women aged <55 years (HR=1.72, 95% CI: 1.27-2.33) and women aged ≥55 (HR=1.74, 95% CI: 1.36-2.22). For ER+ breast cancer, family history was more strongly associated with risk among younger women (HR_{<55}=1.80, 95% CI: 1.66-1.95; HR_{≥55}=1.52, 95% CI: 1.42-1.62; p-value for interaction<0.01). The opposite was true for ER-/PR-/HER2+ breast cancer: although confidence intervals were wide and overlapping, family history was more strongly associated with risk among women aged ≥55 (HR_{<55}=1.27, 95% CI: 0.80-2.01; HR_{≥55}=1.89, 95% CI: 1.24-2.87, p for interaction=0.26). Overall and within each age strata there was no statistical evidence of significant differences between HR estimates for the three tumor subtypes [p-value for homogeneity=0.77, 0.32, and 0.38, in women overall, age <55, and age ≥55, respectively].

Across subtypes, the increased breast cancer risk associated with family history was strongest among women who reported having at least two affected first-degree female relatives (compared to women with no family history: HR_{ER+}=2.05, 95% CI: 1.79-2.36; HR_{ER-/PR-/HER2+}=2.25, 95% CI: 0.99-5.08; HR_{triple-negative}=2.66, 95% CI: 1.66-4.27). Although based on small numbers, and although subtype-specific CI's overlapped, the association between having multiple affected first-degree relatives and breast cancer risk was especially pronounced for the triple-negative subtype. Analyses distinguishing women with a breast cancer family history according to whether any relatives were diagnosed before age 50 did not reveal any significant differences within subtypes. Analysis of partial likelihoods indicated that any observed differences in HR's across subtypes were not statistically significant [p-value (number of affected relatives)=0.87; p-value (age of affected relatives)=0.85].

DISCUSSION

The results of these analyses are consistent with prior studies in indicating that having a history of breast cancer in first-degree relatives is associated with significantly increased breast cancer risk, especially for women with multiple affected first-degree relatives [15,16,19,20]. Here we find that this increased risk is of similar magnitude with respect to ER+, ER-/PR-/HER2+, and triple-negative breast cancer subtypes. Our data indicate a 1.56 to 1.73-fold increased breast cancer risk in women with a first-degree family history and, specifically, a 1.47 to 1.63-fold increased risk of breast cancer in women with one (or more

than one) affected relative and a 2.05 to 2.66-fold increased risk in women with at least two affected relatives, compared to women with no family history.

Certain limitations should be considered when interpreting the results presented here. HER2 status was unknown for 48% of ER-/PR- cases. Excluding these cases from the triple-negative and ER-/PR-/HER2+ case groups could have resulted in some bias: missingness in HER2 varies across BCSC registries and, within registries, could also vary according to patient and tumor characteristics. Although BCSC registry identifiers are not available to investigators outside the Statistical Coordinating Center, we assessed the potential impact of missingness in HER2 status (and other variables) through sensitivity analyses using multiple imputation. Results from these analyses agreed with results from the primary analysis: multiply imputed HR's for the association between first-degree family history and breast cancer risk remained statistically significant and similar in magnitude across subtypes ($HR_{ER+}=1.58$, 95% CI: 1.50-1.65, $HR_{ER-/PR-/HER2+}=1.40$, 95% CI: 1.15-1.70, and $HR_{triple-negative}=1.53$, 95% CI: 1.35-1.73).

Given that this large study cohort was identified from women who had received screening mammography, these results are generalizable to women aged 40-84 years receiving breast imaging screening. As such, the observed distributions of characteristics such as first-degree family history could differ from what would be expected in the absence of such selection criteria: the average number of mammograms received by women who reported a family history was slightly greater than among women reporting no family history (2.57 versus 2.32 mammograms, respectively). Population-based studies of postmenopausal women in the United States have reported prevalence estimates for first-degree family history between 11-13% [21,22], which is modestly different from the 15% reported here. Additionally, while the case population included both screen-detected and interval cases, the study setting could have impacted the distribution of tumor characteristics and case subtypes. The triple-negative subtype in particular may be under-represented in screening populations: given the earlier average age at diagnosis of triple-negative breast cancer [2,7,9,23], women diagnosed with these tumors are likely to have had fewer and less regular screenings prior to diagnosis than women diagnosed with ER+ breast cancer. While prior studies have suggested the triple-negative subtype accounts for 13% to 30% of invasive breast cancers [9,11,23], we found that 11% of cases with complete tumor marker data were triple-negative. The lower prevalence of the triple-negative subtype reported here could also reflect study demographics: the prevalence of this subtype is highest among early-onset breast cancer cases [2,9] and African-American women [2,9], whereas this study was restricted to women aged 40-84 and approximately 7% of cases were African-American.

Although analyses indicated no significant differences across subtypes (both overall and stratified by age), it is possible that greater subtype-specific differences in associations would have emerged had it been possible to include a wider and, specifically, younger age range in the study population. Prior estimates have suggested that 5.3% of women diagnosed with breast cancer before age 40 years carry germ-line mutations in *BRCA1*, compared to 2.2% of cases aged 40-49 and 1.1% of cases aged 50-70 [24]. Thus, if the association between *BRCA1* mutations and triple-negative breast cancer does contribute to a differential association with family history by breast cancer subtype, that difference is likely most apparent among women younger than the age range included here (i.e., 40-84 years).

Having a family history of breast cancer in first-degree relatives is one of the most consistently reported risk factors for breast cancer overall. In the largest study to date, a collaborative reanalysis of more than 58,000 breast cancer cases, women with one affected first-degree relative were found to have a 1.8-fold increased breast cancer risk, while women with two or with three or more affected relatives had a 2.9-fold and a 3.9-fold increased risk,

respectively [15]. The slightly larger magnitude of associations observed in this prior study likely reflects the inclusion of a younger study population than that of the present analysis. In contrast to this earlier study and others not stratified by tumor subtype [15,16,20], we found no difference in breast cancer risk according to the age at diagnosis of affected first-degree relatives. However, this too may reflect the older age range of our study population since studies that find a gradient of increasing risk with decreasing age at diagnosis of first-degree relatives typically note that this gradient is most pronounced with respect to earlier-onset breast cancer [15,16].

While the association between family history and overall breast cancer risk is well-established, previous studies characterizing heterogeneity in the association between family history and risk of different subtypes of breast cancer defined by tumor marker expression have been limited and inconsistent [10,11,25-28]. A prior systematic review of the literature suggested no marked differences in associations with first-degree family history according to hormone receptor status [27]. Jointly stratifying case groups by ER, PR, and HER2 expression status within one of the BCSC registries included in this study, Welsh et al. found that family history was associated with an increased risk of ER+ and ER-/PR-/HER2+ breast cancers but not triple-negative breast cancer; however, those findings were based on a sample size of only 53 triple-negative cases and a shorter duration of follow-up [28]. The two studies to have used a five-marker definition for the basal-like subtype of breast cancer (i.e., triple-negative and cytokeratin 5/6-positive and/or EGFR-positive) have conflictingly reported that family history is most strongly associated with risk of basal-like breast cancer [10] and that there are no differences in associations with family history by molecular subtype [11].

There is considerable evidence to support a predominance of the triple-negative phenotype in *BRCA1*-associated breast cancers [6,7]. Therefore, there is reason to anticipate a higher prevalence of *BRCA1* mutations in women with triple-negative breast cancer than in cases of other tumor types. However, the association between family history and breast cancer risk reflects much more than the contribution of *BRCA1*. Associations between family history and risk of each breast cancer subtype reflect the combined influence of high penetrance mutations (e.g., *BRCA1*, *BRCA2*), mutations of lower penetrance or prevalence (e.g., *ATM*, *TP53*) and susceptibility alleles conferring more moderate risks [29], and associations with the shared environment and lifestyle factors that first-degree relatives often have in common. With the exception of what is known about the association between germ-line mutations in *BRCA1* and the triple-negative subtype, the extent to which these aspects of family history differ in their distribution and role in different breast cancer subtypes remains unknown.

From clinical and biological perspectives, triple-negative breast cancer is a distinct disease. However, aside from the noted link between *BRCA1*-associated breast cancer and the triple-negative phenotype, few risk factors for triple-negative breast cancer have been identified. As the largest study of this relationship to date, the results presented here provide strong evidence that women with a breast cancer family history experience a significantly increased risk of triple-negative breast cancer. However, these results also suggest that the association between first-degree family history of breast cancer and breast cancer risk is similar across subtypes of breast cancer defined on the basis of ER, PR, and HER2 expression.

Acknowledgments

We thank the participating women, mammography facilities, and radiologists for the data they have provided for this study. A list of the BCSC investigators and procedures for requesting BCSC data for research purposes are provided at: <http://breastscreening.cancer.gov/>.

Financial support: This work was supported by a National Cancer Institute-funded Breast Cancer Surveillance Consortium co-operative agreement (U01CA63740, U01CA86076, U01CA86082, U01CA63736, U01CA70013, U01CA69976, U01CA63731, U01CA70040). The collection of cancer data used in this study was supported in part by several state public health departments and cancer registries throughout the U.S. For a full description of these sources, please see: <http://breastscreening.cancer.gov/work/acknowledgement.html>. This publication was supported by grant number T32 CA09168 and R25-CA94880 from the National Cancer Institute, National Institutes of Health. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

Abbreviations

ER	estrogen receptor
PR	progesterone receptor
HR	hazard ratio
CI	confidence interval
BCSC	Breast Cancer Surveillance Consortium
IHC	immunohistochemistry
FISH	fluorescence <i>in situ</i> hybridization

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Table 1

Study population characteristics

	All study subjects		All invasive breast cancers
	N* (%)	Person-years (%)	N* (%)
Age			
40-44	156,525 (15)	721,183 (15)	1,048 (8)
45-49	168,516 (16)	774,589 (16)	1,632 (12)
50-54	175,697 (17)	815,190 (17)	1,942 (14)
55-59	157,556 (15)	685,259 (15)	2,124 (15)
60-64	119,548 (11)	503,219 (11)	1,872 (14)
65-69	92,014 (9)	404,310 (9)	1,591 (12)
70-74	73,671 (7)	339,297 (7)	1,461 (11)
75-79	49,186 (5)	277,553 (6)	1,239 (9)
80-84	27,993 (3)	195,336 (4)	888 (6)
Race / ethnicity			
White non-Hispanic	700,385 (74)	3,182,507 (74)	10,288 (79)
Hispanic white	61,227 (6)	223,331 (6)	535 (4)
African-American	65,990 (7)	267,089 (6)	723 (6)
Asian / Pacific Islander	88,490 (9)	478,274 (11)	1,081 (8)
Other	34,962 (4)	151,497 (4)	397 (3)
Missing	103,412	413,239	773
Education			
≤ High school graduate	251,918 (34)	1,217,548 (33)	3,697 (32)
> High school	498,537 (66)	2,446,537 (67)	7,746 (68)
Missing	304,011	1,051,850	2,354
Prior benign breast procedure			
No	797,548 (80)	3,604,855 (80)	9,466 (72)
Yes	199,110 (20)	881,719 (20)	3,746 (28)
Missing	57,808	229,361	585

* Counts reflect exposure status at the time of the last mammogram during the study period.

Table 2Screening and tumor characteristics by study case group^{*}

	ER+ (N=10,026)	ER-/PR-/HER2+ (N=308)	Triple-Negative (N=705)	X ² p-value [†]
	N (%)	N (%)	N (%)	
Age at most recent mammogram				
40-49	1,919 (19)	61 (20)	163 (23)	<0.01
50-59	2,912 (29)	121 (39)	197 (28)	
60-69	2,524 (25)	71 (23)	185 (26)	
70-84	2,671 (27)	55 (18)	160 (23)	
Histologic subtype				
Ductal	7,203 (74)	262 (91)	597 (92)	<0.01
Lobular	1,028 (11)	6 (2)	11 (2)	
Mixed ductal-lobular	993 (10)	10 (3)	25 (4)	
Other	457 (5)	11 (4)	18 (3)	
Missing	345	19	54	
Stage at diagnosis				
I	5,861 (60)	120 (40)	308 (44)	<0.01
II	3,140 (32)	113 (37)	297 (43)	
III / IV	815 (8)	69 (23)	93 (13)	
Missing	210	6	7	
Grade at diagnosis				
1	2,814 (28)	12 (4)	29 (4)	<0.01
2	4,582 (46)	67 (22)	132 (19)	
3	1,884 (19)	192 (62)	488 (69)	
4	82 (1)	9 (3)	18 (3)	
Missing	664	28	38	

^{*} Triple-negative: ER-negative, PR-negative, HER2-negative[†] P-values chi-square tests comparing the distribution of characteristics across tumor subtypes

Table 3

History of breast cancer in first-degree female relatives and subtype-specific breast cancer risk, by age at start of study follow-up*

TOTAL		ER+ Cases (N=10,026)		ER-/PR-/HER2+ Cases (N=308)		Triple-Negative Cases (N=705)	
N (%)	Person-Years (%)	N (%)	HR (95% CI) [†]	N (%)	HR (95% CI) [†]	N (%)	HR (95% CI) [†]
Overall							
No	816,932 (85)	3,712,949 (86)	7,017 (78)	216 (80)	1.0 (ref)	511 (78)	1.0 (ref)
Yes	132,742 (15)	603,083 (14)	2,004 (22)	53 (20)	1.56 (1.15-2.13)	144 (22)	1.73 (1.43-2.09)
Unknown	104,792	399,903	1,005	39		50	
Age < 55							
No	461,561 (87)	2,043,397 (87)	2,743 (78)	116 (83)	1.0 (ref)	221 (80)	1.0 (ref)
Yes	67,489 (13)	299,150 (13)	760 (22)	23 (17)	1.27 (0.80-2.01)	55 (20)	1.72 (1.27-2.33)
Unknown	55,195	198,016	353	17		23	
Age ≥ 55							
No	355,371 (84)	1,669,553 (85)	4,274 (77)	100 (77)	1.0 (ref)	290 (77)	1.0 (ref)
Yes	65,253 (16)	303,932 (15)	1,244 (23)	30 (23)	1.52 (1.42-1.62)	89 (23)	1.74 (1.36-2.22)
Unknown	49,597	201,888	652	22		27	

* Triple-negative: ER-negative, PR-negative, HER2-negative. Counts reflect exposure status at the time of the last mammogram during the study period.

[†] Adjusted for age at start of follow-up interval (5-year categories), white race, and prior breast procedure.

Table 4

Number and age of first-degree female relatives affected with breast cancer and subtype-specific breast cancer risk*

TOTAL		ER+ Cases		ER-/PR-/HER2+ Cases		Triple-Negative Cases	
N (%)	Person-Years (%)	N (%)	HR (95% CI) [†]	N (%)	HR (95% CI) [†]	N (%)	HR (95% CI) [†]
Number of affected relatives							
No family history	816,932 (86)	3,712,949 (87)	7,017 (79)	1.0 (ref)	216 (82)	1.0 (ref)	511 (79)
<i>Family history:</i>							
≥1 affected relative	118,108 (13)	524,210 (12)	1,689 (19)	1.59 (1.50-1.68)	43 (16)	1.47 (1.05-2.05)	116 (18)
≥2 affected relatives	9,538 (1)	45,173 (1)	211 (2)	2.05 (1.79-2.36)	6 (2)	2.25 (0.99-5.08)	19 (3)
# affected unknown	5,096	33,699	104		4		9
Number of relatives affected at age <50							
No family history	816,932 (89)	3,712,949 (89)	7,017 (82)	1.0 (ref)	216 (83)	1.0 (ref)	511 (82)
<i>Family history:</i>							
None at age <50	55,454 (6)	250,635 (6)	857 (10)	1.67 (1.56-1.80)	26 (10)	1.82 (1.20-2.73)	64 (10)
≥1 at age <50	49,338 (5)	206,295 (5)	653 (8)	1.59 (1.47-1.73)	17 (7)	1.41 (0.85-2.36)	50 (8)
# age <50 unknown	27,950	146,153	494		10		30

* Triple-negative: ER-negative, PR-negative, HER2-negative. Counts reflect exposure status at the time of the last mammogram during the study period. Excludes women with unknown family history (N=104,792 total, 1,005 ER+ cases, 39 ER-/PR-/HER2+ cases, 50 triple-negative cases).

[†] Adjusted for age at start of follow-up interval (5-year categories), white race, and prior breast procedure.