Published in final edited form as:
Breast Cancer Res Treat. 2009 September ; 117(1): 167–176. doi:10.1007/s10549-008-0255-3.

Family history of breast cancer and all-cause mortality after breast cancer diagnosis in the Breast Cancer Family Registry

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Abstract

Background—Although having a family history of breast cancer is a well established breast cancer risk factor, it is not known whether it influences mortality after breast cancer diagnosis.

Methods—Subjects were 4,153 women with first primary incident invasive breast cancer diagnosed between 1991 and 2000, and enrolled in the Breast Cancer Family Registry through population-based

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sampling in Northern California, USA; Ontario, Canada; and Melbourne and Sydney, Australia. Cases were oversampled for younger age at diagnosis and/or family history of breast cancer. Carriers of germline mutations in *BRCA1* or *BRCA2* were excluded. Cases and their relatives completed structured questionnaires assessing breast cancer risk factors and family history of cancer. Cases were followed for a median of 6.5 years, during which 725 deaths occurred. Cox proportional hazards regression was used to evaluate associations between family history of breast cancer at the time of diagnosis and risk of all-cause mortality after breast cancer diagnosis, adjusting for established prognostic factors.

Results—The hazard ratios for all-cause mortality were 0.98 (95% confidence interval [CI] =0.84-1.15) for having at least one first- or second-degree relative with breast cancer, and 0.85 (95% CI=0.70-1.02) for having at least one first-degree relative with breast cancer, compared with having no such family history. Estimates did not vary appreciably when stratified by case or tumor characteristics.

Conclusions—Family history of breast cancer is not associated with all-cause mortality after breast cancer diagnosis for women without a known germline mutation in *BRCA1* or *BRCA2*. Therefore, clinical management should not depend on family history of breast cancer.

Keywords

breast cancer; survival; mortality; family history

Introduction

A family history of breast cancer is a well established risk factor for breast cancer [1-3]. Mutations in known breast cancer susceptibility genes account for only about one-quarter of this familial association [4], so the excess risk still exists for women who do not carry a germline mutation in *BRCA1* or *BRCA2*. It is unclear, however, whether all-cause mortality after breast cancer diagnosis differs between women who do and do not have a family history of breast cancer. A review of studies published between 1976 and 1999 found no consistent evidence of a mortality difference between cases with and without a family history [5], and subsequent studies have generally found no difference with respect to all-cause mortality [6-15] or other outcome measures [9-13,15-21], although some reported a better [22] or worse [23,24] prognosis for cases with a family history of breast cancer. Differences in all-cause mortality between breast cancer cases with and without a family history, should they exist, might be due to differences in biology and, therefore, might give insights into breast cancer etiology, secondary prevention, treatment, and counseling.

Depending on definition, 10% or more of breast cancer cases have a family history of the disease [2]. Having an affected first-degree relative increases risk by an average of about two-fold [1-3]; about 15-20% of this excess risk is explained by germline mutations in *BRCA1* and *BRCA2* [25,26]. Other, lower-penetrance susceptibility genes, as well as shared environmental factors, appear to be responsible for the remaining familial risk [27]. Most previous studies have defined “familial breast cancer” in one of three ways: a self-reported family history of the disease, with variable inclusion of first-, second-, or third-degree relatives; *BRCA1* and/or *BRCA2* linkage within families; or germline *BRCA1* or *BRCA2* mutation carriage in cases [5, 28]. These definitions cover very different scenarios. In this paper, we use the term “familial” to refer to cases with a family history of the disease, and the term “non-*BRCA1/BRCA2*-associated breast cancer” to refer to cases without a known germline mutation in *BRCA1* or *BRCA2*.

Mortality differences between non-*BRCA1/BRCA2*-associated breast cancer cases with and without a family history of breast cancer have not been widely investigated. One Finnish study

[6] and one Dutch study [13] found no differences in overall survival for cases with familial non-*BRCA1/BRCA2*-associated, *BRCA1/BRCA2*-associated, and non-familial breast cancer.

However, neither of these studies was population-based, and both lacked detailed interview data from individual cases, limiting their ability to consider survival associations with other patient characteristics. Furthermore, few prior studies have examined whether any possible association of family history with survival varies by tumor histologic type or hormone receptor status.

It was recently reported by the population-based Ontario Breast Cancer Family Registry (CFR) that all-cause mortality after breast cancer diagnosis did not vary between cases with and without a first-degree family history of breast or ovarian cancer [15]. Here, we expand the sample size and scope of this prior study by including cases from two additional population-based samples from the Northern California and Australian Breast CFRs. If family history were to predict breast cancer survival, then it might influence clinical practice because it can be ascertained prior to treatment. Therefore, using a large, pooled, population-based series of breast cancer cases, we set out to determine whether all-cause mortality in cases with non-*BRCA1/BRCA2*-associated breast cancer varies by family history of breast cancer.

Methods

Study population

This study is based on data from three population-based series of breast cancer cases enrolled in the Breast CFR, an international consortium established in 1995 through funding from the USA National Cancer Institute [29]. Participants include women diagnosed with first primary invasive breast cancer while residing in the San Francisco Bay Area, California, USA; Ontario, Canada; and Melbourne and Sydney, Australia. Each series of incident cases was ascertained through regional population-based cancer registries using the eligibility and sampling criteria described below. Approval of the study protocol was obtained from relevant ethics boards and written informed consent was received from all study participants.

Northern California Breast CFR—Women newly diagnosed with incident breast cancer before the age of 65 years and residing in the nine-county Greater San Francisco Bay Area were identified through the Greater Bay Area Cancer Registry, which ascertains all incident cancers as part of the USA National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program and the California Cancer Registry. A total of 13,301 cases diagnosed between January 1, 1995, and December 30, 2000, were identified. Of these, 12% could not be contacted due to 1) physician refusal (*N*=170; 1%), 2) invalid case contact information (*N*=1,175; 9%), or 3) death (*N*=299; 2%). Of those contacted, 10,641 (91%) completed a brief telephone screening interview on self-reported race/ethnicity and family and personal history of breast, ovarian, and childhood cancer. Cases were eligible to enroll in the family registry if they had characteristics suggesting an inherited susceptibility to breast cancer, namely, diagnosis before age 35 years; bilateral breast cancer and a first diagnosis before age 50 years; prior ovarian or childhood cancer; or a family history of breast, ovarian, or childhood cancer in one or more first-degree relatives. Cases not meeting these criteria were randomly sampled at 5% for non-Hispanic white cases and 20% for cases of any other race/ethnicity. All cases diagnosed between January 1, 1995, and September 30, 1998, were eligible to enroll, whereas enrollment of cases diagnosed between October 1, 1998, and December 30, 2000, was limited to those who self-identified as African-American, Hispanic, Chinese, Japanese, or Filipina. A total of 2,008 cases were invited to enroll in the family registry; of these, 37 were deceased, 402 refused participation, and 1,569 (78%) completed the family history questionnaire by telephone and the risk factor questionnaire by in-person interview. After excluding 76 cases found to have a germline *BRCA1* or *BRCA2* mutation, 182 cases with a prior invasive cancer

other than non-melanoma skin cancer, and 5 cases with no post-interview follow-up, this analysis included 1,306 cases from the Northern California Breast CFR.

Ontario Breast CFR—Women newly diagnosed with incident breast cancer before the age of 69 years between January 1, 1996, and December 31, 1998, who resided in the province of Ontario, Canada, were identified through the Ontario Cancer Registry [30]. All cases younger than age 55 years at diagnosis and a 35% random sample of cases aged 55-69 years were selected (*N*=8,349). Of these, 9% could not be contacted due to 1) physician refusal (*N*=466; 6%), 2) invalid physician contact information (*N*=170; 2%), or 3) death (*N*=136; 2%). Of the 7,577 remaining cases, a mailed screening questionnaire on family history and race/ethnicity was completed for 4,913 (65%), 130 (2%) of whom were deceased; 1,114 (15%) actively refused participation, 1,386 (18%) were non-responders, and 34 (0.5%) could not be contacted. Cases were further selected for inclusion in the family registry if they met certain criteria suggesting increased genetic risk of breast cancer, namely, Ashkenazi Jewish background; prior breast or ovarian cancer; one or more first-degree or two or more second-degree relatives with breast or ovarian cancer; one or more second- or third-degree relatives with breast cancer diagnosed before age 36 years, ovarian cancer diagnosed before age 61 years, multiple primary breast cancers, primary breast and ovarian cancers, or male breast cancer; or three or more first-degree relatives with any combination of breast, ovarian, colon, prostate, and pancreatic cancers and sarcoma, with at least one diagnosis before age 51 years. Cases not meeting these criteria were randomly sampled at 25%. A total of 2,536 cases were selected; of these, 25 (1%) were deceased and 1,835 (72%) completed a telephone interview on detailed family history and a mailed questionnaire on breast cancer risk factors. After excluding 94 cases found to have a germline *BRCA1* or *BRCA2* mutation, 151 cases with a prior invasive cancer other than non-melanoma skin cancer, and 12 cases with no post-interview follow-up, this analysis included 1,578 cases from the Ontario Breast CFR.

Australian Breast CFR—Women newly diagnosed with a first primary invasive breast cancer before the age of 59 years who resided in the metropolitan areas of Melbourne or Sydney at diagnosis were identified through the cancer registries of Victoria and New South Wales, respectively. A total of 4,558 cases were identified, including cases diagnosed in Melbourne between June 1, 1991, and June 30, 1998, or in Sydney between January 1, 1996, and June 30, 1998. All incident cases aged 18-39 years were selected to enroll in the family registry, while those aged 40 years and older were randomly selected at age- and state-dependent rates. In Melbourne, cases aged 40 to 49 years were sampled at 41% and those aged 50 to 59 years were sampled at 25%; in Sydney, cases aged 40 to 59 years were sampled at 28%. Of 2,020 cases selected, 14% could not be contacted due to 1) physician refusal (*N*=240; 12%) or 2) death (*N*=41; 2%). Of the 1,739 cases contacted, information on family history and breast cancer risk factors was collected by in-person interview for 1,360 (78%). After excluding 47 cases with a germline *BRCA1* or *BRCA2* mutation, 29 cases with a prior invasive cancer other than non-melanoma skin cancer, and 15 cases with no post-interview follow-up, this analysis included 1,269 cases from the Australian Breast CFR.

Data collection and follow-up

All cases and consenting relatives completed a structured baseline questionnaire on established and suspected breast cancer risk factors, and cases also completed a questionnaire on family history of cancer in first- and second-degree relatives. We attempted to verify all reports of cancer diagnoses in relatives through pathology review, pathology report, other hospital or clinic records, and/or death certificate. Overall, 45% of breast cancer diagnoses in first-degree relatives and 21% in second-degree relatives were confirmed by at least one of these sources, and were therefore considered to be verified. When self-report by the affected relative was also considered as a basis for confirmation, 99% of diagnoses in first-degree relatives and 98% in

second-degree relatives were verified. Only breast cancers that occurred in relatives prior to the case's date of diagnosis were considered in the definition of a family history.

Breast cancer cases were confirmed by central review of the tumor specimen and pathology report by a Breast CFR pathologist (40%); review of the pathology report only (16%); review of the medical record or cancer registry abstract (29%); or a combination of these methods (15%). Vital status of cases was ascertained through various follow-up activities, including telephone contact with cases or family members (in Australia and Northern California), annual mailed family history follow-up questionnaires (in Ontario), as well as linkage to cancer registry and death registry records, and review of medical records or contact with physician's offices (by all three Breast CFRs). Dates of last follow-up ranged from January 31, 1994, to July 18, 2007, with a median post-interview follow-up time of 6.5 years (interquartile range = 4.6 to 7.7 years). In total, 725 deaths were identified (187 from the Northern California, 255 from the Ontario, and 283 from the Australian Breast CFRs).

BRCA1 and *BRCA2* mutational analyses

Procedures and the validity of methods for detecting germline *BRCA1* and *BRCA2* mutations have been described in detail elsewhere [31]. Briefly, mutational analyses were undertaken on 83% of cases by laboratories affiliated with the Breast CFRs and at Myriad Genetic Laboratories, Inc. Previously validated [31,32] methods used were two-dimensional gene scanning, denaturing high-performance liquid chromatography, enzymatic mutation detection, protein truncation tests, and exon grouping analysis; full sequence analysis was also conducted more recently. Carriers of germline *BRCA1* or *BRCA2* mutations were identified for a separate study, as their prognostic factors may differ from those of non-carriers.

Statistical analysis

Multivariable Cox proportional hazards regression, with days since interview as the time scale, was used to analyze associations between all-cause mortality after breast cancer diagnosis and a family history of breast cancer. Follow-up time was left-truncated at the date of interview to prevent potential bias due to differential mortality between diagnosis and interview. Relative risks of all-cause mortality were estimated as hazard ratios (HR) with 95% confidence intervals (CI). Wald tests for trend were used to evaluate associations with an increasing number of affected relatives with breast cancer.

Models were adjusted for age at diagnosis (continuous years), race/ethnicity (white, black, Hispanic, Asian, other, or unknown), Breast CFR center (Northern California, Ontario, or Australia), and tumor characteristics significantly associated with breast cancer mortality, including size (≤20 mm, >20 mm, or unknown), number of affected lymph nodes (0, 1-3, ≥4, or unknown), grade (1, 2, 3, or unknown), histology (invasive ductal, invasive lobular, other, or unknown), estrogen receptor (ER) status (negative, positive, or unknown), and progesterone receptor (PR) status (negative, positive, or unknown). A secondary analysis was conducted with additional adjustment for treatment with chemotherapy (yes, no, or unknown) or tamoxifen (yes, no, or unknown). Further adjustment for other characteristics, such as level of education, body mass index, recent physical activity, parity, age at first birth, time between last full-term pregnancy and diagnosis, and other treatment types, did not affect the results; therefore, these variables were not included in the final multivariable models. The proportional hazards assumption was tested for all covariates using significance tests of interactions with the time scale, and visual examination of Kaplan-Meier plots and scaled Schoenfeld residual plots. Several variables, not including family history, violated the assumption of proportional hazards. However, there was no difference in the association with family history comparing models with and without time-covariate interaction terms, so the results of models without these interactions are presented.

We performed subgroup analyses according to the earliest age at breast cancer diagnosis for an affected relative (<40, 40-49, 50-59, or ≥60 years), and also stratified analyses by the case's age at diagnosis (<40 or ≥40 years), tumor size, number of affected lymph nodes, tumor grade, tumor histology, ER status, PR status, and Breast CFR. Tests for heterogeneity across strata were conducted using likelihood ratio tests comparing nested models with and without an interaction term with family history. All analyses were conducted first including all reported familial diagnoses of breast cancer, then with only verified diagnoses (using both definitions described above). *P* values ≤0.05 were considered statistically significant, and all tests of significance were two-sided. Analyses were performed using SAS Version 9.1 (SAS Institute, Cary, NC).

Results

Of the 4,153 cases, 1,112 (27%) reported a first-degree and 1,871 (45%) reported a first- or second-degree family history of breast cancer (Table 1). The distributions of other personal and tumor characteristics of the cases are shown in Table 1. Cases with a first- or second-degree family history of breast cancer were older and more likely to be from Ontario or Northern California (versus Australia) than cases without such a history, reflecting different sampling strategies, but did not differ in tumor characteristics after adjustment for age and CFR (data not shown).

The results in Table 2 show no evidence that all-cause mortality after breast cancer diagnosis differed between cases with and without a family history of breast cancer. The HR for having one or more first- or second-degree relatives with a history of breast cancer at the time of diagnosis was 0.98 (95% CI =0.84-1.15), and there was no dose-response trend with an increasing number of affected relatives (P_{trend}=0.98). Similarly, there was no apparent difference in all-cause mortality between cases who did and did not have one or more first-degree relatives with a history of breast cancer at diagnosis (HR=0.85, 95% CI=0.70-1.02). Again, there was no evidence of an association between increasing number of affected relatives and all-cause mortality (P_{trend}=0.14). The HR did not differ appreciably between cases who had one first-degree relative with breast cancer at the time of diagnosis (HR=0.83, 95% CI=0.68-1.02) and cases who had two or more such relatives (HR=0.98, 95% CI=0.57-1.68), although the latter estimate was based on only 14 cases.

Secondary analyses revealed no substantial differences in the HR when cases were categorized according to youngest age at diagnosis of breast cancer in a first-degree relative. There was a marginal inverse association with all-cause mortality for cases with one or more first-degree relatives diagnosed with breast cancer at age 60 years or older (37%, the largest subgroup of cases; HR=0.71, 95% CI=0.53-0.96). However, there was no association between all-cause mortality and having first-degree relatives diagnosed with breast cancer before age 40 years (HR=1.14, 95% CI=0.76-1.71), between 40 and 49 years (HR=0.99, 95% CI=0.73-1.34), or between 50 and 59 years (HR=1.16, 95% CI=0.85-1.58).

In exploratory stratified analyses of the association between all-cause mortality and a first-degree family history of breast cancer (Table 3), a nominally significant inverse association with family history was observed for cases with 1-3 affected lymph nodes and those with grade 2 tumors. However, there was no association with family history for most case subgroups and there was no significant heterogeneity in family history association across any strata. Results did not change appreciably after additional adjustment for treatment with chemotherapy or tamoxifen. For instance, the treatment-adjusted HR for having one or more first- or second-degree relatives with a history of breast cancer was 0.95 (95% CI=0.81-1.11). Likewise, results were unchanged when 58 cases with known metastatic disease were excluded or when only verified cancers in relatives were considered, although numbers were small for analyses

including only diagnoses confirmed by medical or death records (32% of diagnoses in relatives; data not shown).

Discussion

From this large study combining incident breast cancer cases from population-based breast cancer family registries in three different countries, we found no evidence that risk of all-cause mortality varied between breast cancer cases with and without a family history of breast cancer. Our results did not vary substantially by age at diagnosis of an affected relative or by the case's age, country of residence, or tumor characteristics. Thus, our results are generally consistent with the majority of prior studies, which did not find mortality differences between breast cancer cases with and without a family history of breast cancer [5-15].

Some studies have found that breast cancer cases with a family history are more likely to have smaller and earlier-stage tumors [15,33] and to have been diagnosed by mammography [15, 33-35]. We observed no difference in the number of affected nodes, tumor grade, or tumor size between cases with and without a family history, nor did we find evidence that the relationship between family history and all-cause mortality varied by these tumor characteristics. Adjusting for treatment, level of education, body mass index, physical activity, or reproductive characteristics also did not alter our results.

Reliability of self-reported breast cancer in first-degree relatives is generally very high, although diagnoses for second-degree relatives may be under-reported [36-40]. Although unlikely, if such under-reporting differed by subsequent mortality of cases in our study, it could have contributed to the lack of an observed association with a first- or second-degree family history of breast cancer. We might also have been unable to detect some associations due to the small sample size of some case subgroups.

Survival bias is of minimal concern in the present study, given that only 3-5% of potential participants were deceased at the time of enrollment, and follow-up time was left-truncated at the date of interview. In addition, selection bias due to differential follow-up was minimized by the use of linkages to population-based cancer registry and death registry records to track outcomes for nearly all cases. By limiting our study sample to cases without detected germline *BRCA1* or *BRCA2* mutations, we focused on the clinically important subset of familial breast cancer that is not attributable to rare, high-penetrance mutations in these genes. Non-*BRCA1/BRCA2*-associated breast tumors tend to be of lower grade than *BRCA1/BRCA2*-associated tumors and are morphologically and immunohistologically distinct [41-43], with features that would generally be expected to indicate a better prognosis. However, phenotypic differences between familial and sporadic breast tumors have not been established.

The present study has several other strengths, including the large sample size, population-based design, high-quality clinical and interview data, and independent confirmation of 99% of all reported familial diagnoses. All of the Breast CFRs over-sampled cases with particular genetic risk indicators, thereby increasing the number of cases with a family history. In addition, the three study sites used standardized questionnaires and data dictionaries, which allowed comparability and uniform adjustment for confounders across the three Breast CFRs. Although there were some differences in selection criteria and enrollment procedures, our findings did not differ by Breast CFR.

In summary, a family history of breast cancer does not appear to influence all-cause mortality for women with non-*BRCA1/BRCA2*-associated breast cancer. Thus, although a family history of breast cancer is known to increase the risk of developing the disease, women with such a family history can be reassured that their mortality risk is similar to that of affected women without a family history. Our results suggest that the clinical management of breast cancer for

women without a germline mutation in *BRCA1* or *BRCA2* should not be influenced by family history status.

Acknowledgments

The authors would like to thank the thousands of women and their families who participated in this research. We also thank Enid Satariano and Jocelyn Koo (Northern California Cancer Center), Gordon Glendon and Elaine Maloney (Cancer Care Ontario), and Maggie Angelakos (University of Melbourne) for their assistance. The Breast Cancer Family Registry (Breast CFR) was supported by the National Cancer Institute, National Institutes of Health under RFA CA-95-011 and CA-06-503, and through cooperative agreements with members of the Breast CFR and P.I.s. The three Breast CFRs contributing data to this analysis were supported by U01 CA69417 (Northern California Cancer Center), U01 CA69467 (Cancer Care Ontario), and U01 CA69638 (University of Melbourne). The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Breast CFR, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government or the Breast CFR.

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Table 1

Personal and disease characteristics of cases (*N*=4153) by Breast Cancer Family Registry

	All N=4153		Ontario N=1578		Northern California N=1306		Australia N=1269	
	N	%	N	%	N	%	N	%
Age at diagnosis (years)								
<35	542	13	135	9	191	15	216	17
35-39	578	14	146	9	74	6	358	28
40-44	558	13	224	14	167	13	167	13
45-49	776	19	348	22	241	19	187	15
50-54	784	19	371	24	229	18	184	15
55-59	474	11	135	9	182	14	157	12
≥60	441	11	219	14	222	17	0	0
Mean	47		43		49		48	
Race/ethnicity								
White	3133	76	1457	92	542	42	1134	89
Black	209	5	8	1	201	15	0	0
Hispanic	221	5	0	0	221	17	0	0
Asian	452	11	52	3	326	25	74	6
Other	79	2	47	3	16	1	16	1
Unknown	59	1	14	1	0	0	45	4
Number of affected lymph nodes								
None	2242	54	823	52	740	57	679	54
1-3	976	23	377	24	286	22	313	25
≥4	495	12	163	10	159	12	173	14
Unknown	440	11	215	14	121	9	104	8
Mean	2		2		1		2	
Tumor size (mm)								
≤20	2579	62	941	60	786	60	852	67
>20	1303	31	505	32	440	34	358	28
Unknown	271	7	132	8	80	6	59	5
Mean	21		20		20		22	

	All N=4153		Ontario N=1578		Northern California N=1306		Australia N=1269	
	N	%	N	%	N	%	N	%
Tumor grade								
1	788	19	312	20	291	22	185	15
2	1518	36	590	37	477	37	451	36
3	1522	37	554	35	407	31	561	44
Unknown	325	8	122	8	131	10	72	6
Histologic type								
Ductal	3402	82	1372	87	1088	83	942	74
Lobular	245	6	102	7	53	4	90	7
Other	296	7	61	4	165	13	70	6
Unknown	210	5	43	3	0	0	167	13
Estrogen receptor status								
Negative	1002	24	323	21	287	22	392	31
Positive	2717	65	1029	65	900	69	788	62
Unknown	434	11	226	14	119	9	89	7
Progesterone receptor status								
Negative	1094	26	369	23	372	29	353	28
Positive	2602	63	968	61	808	62	826	65
Unknown	457	11	241	15	126	10	90	7
Chemotherapy								
No	1404	34	583	37	461	35	360	28
Yes	2024	49	674	43	806	62	544	43
Unknown	725	18	321	20	39	3	365	29
Tamoxifen								
No	1945	47	668	42	555	42	722	57
Yes	1623	39	576	37	742	57	305	24
Unknown	585	14	334	21	9	1	242	19
Family history of breast cancer*								
None	2282	55	772	49	627	48	883	70

	All N=4153		Ontario N=1578		Northern California N=1306		Australia N=1269	
	N	%	N	%	N	%	N	%
First-degree	1112	27	453	29	524	40	135	11
Second-degree	759	18	353	22	155	12	251	20

*Based on self-report

Table 2

Hazard ratio (HR) estimates and 95% confidence intervals (CI) of associations between family history of breast cancer and all-cause mortality

	Deaths (*N*)	HR* (95% CI)
First-or second-degree relatives		
None	424	1.00
≥1	301	0.98 (0.84-1.15) p = 0.82
None	424	
1	200	1.00
≥2	101	0.97 (0.81-1.15) 1.02 (0.81-1.28) p_{trend} = 0.98
First-degree relatives		
None	578	1.00
≥1	147	0.85 (0.70-1.02) p = 0.09
None	578	
1	133	1.00
≥2	14	0.83 (0.68-1.02) 0.98 (0.57-1.68) p_{trend} = 0.14

*Adjusted for age, Breast CFR center, race/ethnicity, number of affected lymph nodes, tumor size, tumor grade, histologic type, estrogen receptor status, and progesterone receptor status

Table 3

Stratified hazard ratio (HR) estimates and 95% confidence intervals (CI) of associations between family history of breast cancer and all-cause mortality

Proband or tumor characteristic	First-degree relatives	Deaths (*N*)	HR* (95% CI)	$P_{heterogeneity}$
Age at diagnosis <40 years	None	264	0.86 (0.58-1.27)	
	≥1	29	p = 0.44	
Age at diagnosis ≥40 years	None	314	0.84 (0.67-1.05)	
	≥1	118	p = 0.13	0.92
No affected lymph nodes	None	156	1.08 (0.77-1.51)	
	≥1	54	p = 0.65	
1-3 affected lymph nodes	None	196	0.64 (0.44-0.93)	
	≥1	34	p = 0.02	
≥4 affected lymph nodes	None	144	1.03 (0.70-1.52)	
	≥1	42	p = 0.87	0.20
Tumor size ≤20 mm	None	261	0.93 (0.71-1.21)	
	≥1	79	p = 0.58	
Tumor size >20 mm	None	260	0.77 (0.57-1.05)	
	≥1	58	p = 0.10	0.41
Tumor grade 1	None	36	0.93 (0.47-1.85)	
	≥1	14	p = 0.83	
Tumor grade 2	None	182	0.69 (0.48-0.98)	
	≥1	41	p = 0.04	
Tumor grade 3	None	316	0.98 (0.75-1.27)	
	≥1	79	p = 0.85	0.38
Ductal	None	489	0.85 (0.67-1.04)	
	≥1	126	p = 0.12	
Lobular	None	38	0.67 (0.30-1.51)	
	≥1	9	p = 0.34	
Other	None	23	0.90 (0.37-2.20)	
	≥1	9	p = 0.82	0.34
Estrogen-receptor-negative	None	194	0.81 (0.57-1.15)	
	≥1	43	p = 0.24	
Estrogen-receptor-positive	None	313	0.95 (0.74-1.22)	
	≥1	96	p = 0.69	0.34
Progesterone-receptor-negative	None	187	0.99 (0.72-1.38)	
	≥1	54	p = 0.99	
Progesterone-receptor-positive	None	318	0.84 (0.65-1.09)	

Proband or tumor characteristic	First-degree relatives	Deaths (*N*)	HR* (95% CI)	$P_{heterogeneity}$
	≥1	84	p = 0.19	0.59
Ontario	None	198	0.77 (0.57-1.03)	
	≥1	57	p = 0.08	
Northern California	None	122	0.84 (0.61-1.17)	
	≥1	65	p = 0.30	
Australia	None	258	0.87 (0.57-1.31)	
	≥1	25	p = 0.49	0.82

*Adjusted for age, Breast CFR center, race/ethnicity, number of affected lymph nodes, tumor size, tumor grade, histologic type, estrogen receptor status, and progesterone receptor status