Research Article

Cancer Epidemiology, Biomarkers & Prevention

Family History of Breast Cancer in Relation to Tumor Characteristics and Mortality in a Population-Based Study of Young Women with Invasive Breast Cancer

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Abstract

Background: Inherited predisposition may be associated with distinctive breast cancer phenotypes and/or mortality. Past studies have had inconsistent results and little is known about the contributions of screening and treatment.

Methods: Within a population-based cohort of 1,260 women diagnosed with invasive breast cancer before age 46, we assessed how family history of breast cancer relates to mortality and tumor characteristics. Analyses were repeated excluding *BRCA1/BRCA2* carriers. Medical records were reviewed for treatment history and tumors were centrally reviewed and tested. Cox proportional hazard modeling was used to assess the risk of dying in relation to family history; logistic regression was used to assess the association of family history to tumor characteristics.

Results: Compared with women with no family history, women with first-degree family history of breast cancer had a 40% reduction (95% CI: 0.5–0.8) in the risk of dying. Mortality in women with only a second-degree family history was similar to those with no family history. The risk of dying was further reduced in those with a greater number of affected relatives. These relationships did not seem to be attributable to differences in screening, detection method, or treatment. Tumors in women with a first-degree family history had generally more favorable prognostic profiles.

Conclusion: Our findings suggest that breast cancer patients with a first-degree family history, compared with their counterparts without such a profile, may have a better prognosis.

Impact: These findings support the need for future research directed at replicating these results and identifying factors underlying this possible relationship. *Cancer Epidemiol Biomarkers Prev; 20(12); 2560–71. ©2011 AACR.*

Introduction

It has been hypothesized that breast cancers in women with an inherited predisposition to breast cancer are phenotypically and prognostically distinct. Although family history is a well-established etiologic risk factor for breast cancer, its relationship with survival remains unclear. A number of studies have observed improved survival for women with a positive family history (1–8) whereas others report little or no difference (9–15) or worse survival (16–18). Few studies have been population based (6, 8, 11, 15, 18, 19); most have been set within single institutions, specialty clinics, or high-risk family settings and may not include the wider spectrum of breast cancer and family history found in the general population. Studies of tumor characteristics and prognosis have yielded mixed results (20–28), and most prior work has been conducted in selected populations, particularly high-risk families. The lack of cohesion in results has been noted and recommendations have been made to examine these questions in population-based settings with careful consideration of age and comparison groups (29).

This study investigates the extent to which family history of breast cancer relates to tumor features and mortality in a population-based cohort of young women with invasive breast cancer and assesses the extent to which associations are accounted for by differences in screening or treatment according to family history.

Methods

Study population

A population-based cohort of women with invasive breast cancer was ascertained through the Cancer

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doi: 10.1158/1055-9965.EPI-11-0781

Surveillance System (CSS) of Western Washington, a participant in the Surveillance Epidemiology and End Results (SEER) Cancer Registry Program of the National Cancer Institute (30). Cases were women with a first primary, invasive breast cancer who originally completed in-person interviews for 2 population-based case–control studies of breast cancer, both of which have been previously described (31, 32). The first study ascertained all breast cancer cases diagnosed on January 1, 1983 to April 30, 1990 in Caucasian women born after 1944 who were residents of King, Pierce, and Snohomish counties at diagnosis. The second study ascertained all cases diagnosed before age 45 from May 1, 1990 to December 31, 1992 among women of all races in the same 3 counties. Both studies used standardized in-person interviews that elicited information in a comparable format. Interviews were completed on 83.6% ($n = 747$) of those eligible in the first study and 83.9% ($n = 539$) in the second study. Follow-up of this cohort of 1,286 was initiated to investigate factors affecting survival in young women with invasive breast cancer. Participants signed consent forms for the original and subsequent studies. The Fred Hutchinson Cancer Research Center Institutional Review Board approved all aspects of this research.

Interview and medical record data

Information on risk factors for breast cancer and a detailed family history of cancer for the period preceding diagnosis was obtained through a structured in-person interview which included enumeration of all first (mother, sisters)- and second (aunts, grandmothers)-degree female blood relatives, followed by questions on each relative about birth and death year, and cancer history. Cohort members (or proxies) were recontacted beginning in 1993 to collect information on treatment and selected postdiagnosis exposures. The initial follow-up survey was completed for 1,157 (90.0%) cohort members (212 were proxy interviews). Information on tumor size, nodal status, stage, method of detection, and treatment was obtained through a detailed medical record review which was completed on 1,127 (87.6%) women. CSS data were used as the source of information on clinical factors when medical record review was not possible.

Tissue collection, pathology review, and tumor marker analyses

Paraffin-embedded preadjuvant therapy primary breast tumor samples were collected from area pathology laboratories. A single pathologist (PLP) conducted a centralized histopathologic review of all available tumor blocks or slides ($n = 1,019$ or 79.2%). Tumor tissue sufficient for immunohistochemical (IHC) analyses was available on 907 (70.5%) women. Protein expression of estrogen receptor (ER), progesterone receptor (PR), p53, Ki-67 proliferation–related antigen, HER-2, cyclin E, p27, and BCL-2 was assessed with immunoperoxidase assays as described previously (33). Antibody scoring protocols involved a subjective interpretation of staining intensity and/or the percentage of positive tumor cells and incorporated known expression patterns and cellular locations of proteins. For ER/PR, any staining above negative was considered positive; negative and low intensity BCL-2 stains were classified as "low" and intermediate/high staining was classified as "high;" Ki-67 proliferation index was computed as the average of the ratios of Ki-67–positive cells over 4 high powered fields with 25% or above considered high proliferation and less than 25% classified as "low;" any nuclear staining of tumor cells for p53 was considered positive; negative and "1+" staining for HER-2 were classified as negative, and "2+" and "3+" were considered positive; cyclin E and p27 expression were classified on a scale of 1 (negative) to 7 (highest intensity), with values of 1 to 4 classified as low and 5 to 7 classified as high for cyclin E, and values of 1 to 2 classified as low and 3 to 7 classified as high for p27. Positive and negative controls were included in each assay series; antibody batches were titered against known controls to assure standard testing over time.

BRCA1 and *BRCA2* genotyping

BRCA1 and *BRCA2* genotyping was conducted as part of a prior study with lymphocytes from women with either a first-degree family history of breast cancer or a diagnosis of breast cancer before age 35, 2 hallmarks of an increased likelihood of carrying a *BRCA1*/*BRCA2* mutation (34, 35). Altogether, 323 cases in this cohort meeting either or both of these criteria were genotyped with single-strand conformational polymorphism (SSCP) followed by direct sequencing of all variant bands occurring in less than 5% of samples and supplemented with novel primers designed to provide redundant coverage in some regions, as previously described (34–36). The proportions genotyped did not vary by age or family history; a higher proportion of genotyped cases were alive at last follow-up and fewer had advanced stage disease than nongenotyped cases, due largely to a lag between interview and blood collection in the first case–control study. Analyses herein included data only on *BRCA1*/*BRCA2* mutations identified clearly as disease associated (34, 35). The pathology and genotyping laboratories were blinded with regard to risk factors, treatment history, and vital status.

Follow-up for mortality

The CSS follows all cancer cases for vital status, including those who move outside of the area, through annual contact with follow-up physicians and linkage with databases such as the Washington State death files and the National Death Index. Vital status was also updated through ongoing contacts with the women (or proxies). Follow-up ended in April 2009, by which time 34.1% ($n = 438$) of the 1,286 cohort members had died. Of 848 women not reported to be dead as of April 2009, 97.4% were verified as alive within the preceding 12-month period and 99.8% were located within the preceding 36-month period. Overall, the mean and median follow-up

periods accrued for living cohort members were respectively 19.8 and 19.3 years.

Statistical analyses

Cox proportional hazard modeling was used to estimate the relative risk (HR) of death associated with clinical characteristics and family history. Analyses considered both all-cause- and breast cancer mortality. Deaths not attributable to breast cancer were rare (88.4% of 438 deaths were confirmed as breast cancer related) and results were similar using both outcomes; herein, we present all-cause mortality. Cohort members were followed until the earliest of the date of death, date last known to be alive, or the end of follow-up. Results were similar using 2 endpoints, 10-year survival and survival through April, 2009; we present results for survival through April, 2009.

To account for the left truncation of survival times (women had to survive a minimum interval postdiagnosis to complete the original interview), we conditioned on the probability that a woman survived to time of interview (37). Unconditional logistic regression was used to obtain estimates of the relative risk (as estimated by the ORs and 95% CIs) for associations between indicators of inherited predisposition and tumor characteristics. Analyses were conducted with the statistical packages Stata (Stata Corporation) and SAS (SAS Institute Inc.).

All analyses accounted for the effects of age (continuous) and diagnosis year (exact). The following factors were evaluated for potential confounding of survival analyses on the basis of a 10% magnitude changes in risk estimates: race (white and nonwhite), smoking (ever and never), alcohol use (average lifetime weekly number of drinks), oral contraceptive use (ever and never), parity (nulliparous and parous), time since last birth, body mass index (kg/m^2 in quartiles), number of relatives at risk, mammogram history (ever/never, frequency in 5 years before diagnosis), method of detection (screening mammography, clinical breast exam, self/partner, and other), stage, tumor size, and nodal status. Potential confounding by treatment was assessed for surgery, radiation therapy (ever/never), chemotherapy (ever/never), hormone therapy (ever/never), and use of either of 2 commonly prescribed combination chemotherapy regimens [CAF: cyclophosphamide/doxorubicin/5-fluorouracil; CMF: cyclophosphamide/methotrexate/5-fluorouracil (83% of cases who received chemotherapy received one or the other)]. These factors were further tested for potential modifying effects on the association between family history and mortality. The distant and regional stage categories had to be combined for some analyses because of the small numbers of both distant stage cases overall ($n = 24$) and distant stage cases still alive at end of follow-up ($n = 1$). Similarly, women with varying numbers of affected nodes had to be combined into a positive node group for some analyses. To assess the effect of family history in the context of other accepted clinical predictors of mortality, a final multivariate model examined the influence of family history on mortality after accounting for age, year of diagnosis, tumor size, nodal status, grade, and ER/PR/HER2 status. Twenty-six adopted women were excluded, resulting in a final analysis cohort of 1,260 women. Fifteen women with at least one first-degree relative with unknown cancer status and no known breast cancer affected relatives (1.2%) were excluded from analyses of family history. In addition, 204 women (16%) without any known affected relatives had at least one second-degree relative with an unknown breast cancer status; for most of these women, cancer history was complete for all but 1 ($n = 126$) or 2 ($n = 36$) second-degree relatives. Analyses of family history were conducted 2 ways with identical results: excluding these 204 women and including them in the group with no family history; results presented here include these 204 women in the no family history group. For analyses of family history in relation to mortality and to tumor features, we considered effects both including and excluding women with mutations in *BRCA1* or *BRCA2*, with similar results.

Results

A description of the relationship of clinical and demographic characteristics to mortality is presented in Table 1. Advanced stage, larger tumor size, positive nodal status, bilateral breast cancer, and early year of diagnosis were associated with an increased risk of dying. History of a mammogram was associated with a reduced risk of dying.

The distribution of clinical characteristics according to family history is shown in Table 2. Similar proportions of women with a first-degree and second-degree only family history of breast cancer were diagnosed with local stage disease (60.7% and 61.1%), whereas the proportion was slightly lower (55.1%) in women with no family history of breast cancer. Results for nodal status were similar to those for stage. Women with a first-degree family history had the highest portion of small ($\leq$2 cm) tumors (58.3%), and women with only a second-degree family history and no family history had smaller proportions with a small tumor (51.2% and 50.6%, respectively). A higher proportion of women with a first-degree family history reported a mammogram in the preceding 5 years (56.3%) than women with only a second-degree family history (42.3%) and no family history (31.2%). Women with a family history were more likely to have had their breast cancer detected by screening mammogram (14.5% in first degree and 11.2% in second degree compared with 9.8% in those with no family history).

Women with a first-degree family history of breast cancer had a 40% reduction in the risk of dying compared with women with no family history (95% CI: 0.5–0.8). The presence of only a second-degree family history did not influence the risk of dying (HR: 0.9; 95% CI: 0.8–1.2; Table 3). The risk of dying was similarly decreased for cases with an affected mother (HR: 0.6; 95% CI: 0.4–0.8) or sister (HR: 0.5; 95% CI: 0.3–0.9), and the absence of an effect associated with having only a second-degree family

Table 1. Relative risk of dying in relation to clinical characteristics among 1,260 nonadopted women diagnosed with invasive breast cancer in 1983 to 1992 at age 45 or younger

Characteristic	Alive *N* = 833 *N* (%)	Deceased *N* = 427 *N* (%)	Age and year of diagnosis adjusted HR (95% CI)	Multivariate adjusted[a] HR[a] (95% CI)
Age at diagnosis				
21–34	159 (59.8)	107 (40.2)	1.0 (Ref.)	1.0 (Ref.)
35–40	310 (64.4)	171 (35.6)	0.8 (0.5–1.2)	0.8 (0.5–1.2)
41–45	364 (71.0)	149 (29.0)	0.6 (0.3–1.2)	0.6 (0.4–1.2)
Year of diagnosis				
1983–1986	150 (55.1)	122 (44.9)	1.0 (Ref.)	1.0 (Ref.)
1987–1989	280 (67.8)	133 (32.2)	0.5 (0.4–0.8)	0.6 (0.4–0.9)
1990–1992	403 (70.1)	172 (29.9)	0.4 (0.2–0.9)	0.4 (0.2–0.9)
Stage of disease (SEER stage)				
Local	555 (77.2)	164 (22.8)	1.0 (Ref.)	1.0 (Ref.)
Regional	271 (53.8)	233 (46.2)	2.4 (2.0–2.9)	2.4 (2.0–2.9)
Distant	1 (4.2)	23 (95.8)	21.8 (13.9–34.1)	21.8 (13.9–34.3)
Tumor size (cm)				
≤2	482 (75.0)	161 (25.0)	1.0 (Ref.)	1.0 (Ref.)
>2–5	288 (59.3)	198 (40.7)	1.8 (1.5–2.2)	1.5 (1.2–1.8)
>5	46 (45.5)	55 (54.5)	2.8 (2.1–3.8)	2.0 (1.4–2.8)
Nodal status				
Negative	560 (76.9)	168 (23.1)	1.0 (Ref.)	1.0 (Ref.)
1 Positive node	89 (67.4)	43 (32.6)	1.6 (1.2–2.3)	1.5 (1.1–2.1)
2 Positive node	34 (50.7)	33 (49.3)	2.7 (1.8–3.9)	2.7 (1.8–3.9)
3+ Positive node	78 (42.6)	105 (57.4)	3.6 (2.8–4.6)	3.1 (2.4–4.0)
Unknown # positive node	69 (52.3)	63 (47.7)	2.0 (1.5–2.7)	1.7 (1.2–2.4)
Laterality of breast cancer				
Unilateral only	779 (967.6)	374 (32.4)	1.0 (Ref.)	1.0 (Ref.)
Bilateral	54 (50.5)	53 (49.5)	1.5 (1.1–2.0)	1.6 (1.2–2.2)
Mammograms in 5 years before diagnosis date				
None	456 (61.9)	281 (38.1)	1.0 (Ref.)	1.0 (Ref.)
0 in last 5 years	27 (73.0)	10 (27.0)	0.7 (0.4–1.3)	0.7 (0.4–1.4)
1–2	257 (70.2)	109 (29.8)	0.8 (0.6–1.0)	0.8 (0.7–1.1)
3+	93 (78.2)	26 (21.8)	0.6 (0.4–0.9)	0.6 (0.4–0.9)

[a]Multivariate-adjusted HRs are adjusted for age at diagnosis (continuous), year of diagnosis (exact), and other characteristics in the table, with the following exceptions. Stage is not adjusted for size and nodal status. Size and nodal status are not adjusted for stage because each of them comprises part of staging.

history was consistent across cases with affected aunts versus grandmothers and maternal versus paternal side relatives (data not shown). The risk of dying was lower in women with greater numbers of affected relatives (P_{trend} = 0.05) and slightly lower in women with a relative diagnosed before age 45. Neither family history of bilateral disease nor family history of ovarian cancer had any effect on the risk of dying (data not shown).

The associations involving family history could not be ascribed to mutations in *BRCA1* and *BRCA2*, as results were unchanged by exclusion of carriers (Table 3). Associations were also unchanged following adjustment for stage, tumor size, nodal status, mammography history, method of detection, body mass index, recency of last birth [the latter 2 factors influence the risk of dying in this cohort, as previously reported (33, 38)], education, income, race, smoking, alcohol intake, surgery type, radiotherapy, chemotherapy, hormonal therapy, or treatment combinations. There was little or no evidence of effect modification by clinical characteristics or treatment (Table 4).

The tumors of women with a first-degree family history had a somewhat more favorable prognostic profile than those in women with no or only a second-degree family history (Table 5). Associations were similar when we included and excluded *BRCA1/2* mutation carriers; results presented exclude carriers. Compared with women with no family history, tumors in women with first-degree family history were less likely to be large in size. Tumors in these women were also less likely to be in the higher risk

Table 2. Clinical characteristics according to family history of breast cancer

Characteristic	No family history *N* = 723 *N* (%)	First-degree family history *N* = 222 *N* (%)	Second-degree family history *N* = 300 *N* (%)
Stage of disease (SEER stage)			
Local	394 (55.1)	133 (60.7)	182 (61.1)
Regional	303 (42.4)	83 (37.9)	113 (37.9)
Distant	18 (2.5)	3 (1.4)	3 (1.0)
Tumor size (cm)			
≤2	358 (50.6)	127 (58.3)	149 (51.2)
>2–5	288 (40.7)	82 (37.6)	114 (39.2)
>5	62 (8.8)	9 (4.1)	28 (9.6)
Nodal status			
Negative	402 (56.5)	133 (60.5)	183 (62.0)
1 Positive node	77 (10.8)	26 (11.8)	29 (9.8)
2 Positive node	38 (5.3)	7 (3.2)	21 (7.1)
3+ Positive node	122 (17.1)	25 (11.4)	32 (10.8)
Unknown # positive node	73 (10.3)	29 (13.2)	30 (10.2)
Mammograms in prior 5 years			
None	476 (65.9)	90 (40.5)	164 (54.7)
0 in last 5 years	21 (2.9)	7 (3.2)	9 (3.0)
1–2	173 (24.0)	84 (37.8)	103 (34.3)
3+	52 (7.2)	41 (18.5)	24 (8.0)
Surgical treatment			
None/biopsy only	7 (1.0)	0 (—)	5 (1.7)
Lumpectomy/tylectomy	304 (42.1)	88 (39.60	131 (3.7)
Mastectomy	411 (56.9)	134 (60.4)	164 (54.7)
Radiation/chemotherapy			
Neither	97 (13.6)	37 (17.1)	41 (13.9)
Chemotherapy only	248 (34.8)	68 (31.3)	89 (30.2)
Radiation only	116 (16.3)	35 (16.1)	59 (20.0)
Radiation + chemotherapy	252 (35.3)	77 (35.5)	106 (35.9)
CAF or CMF chemotherapy			
No chemotherapy	213 (29.7)	72 (33.0)	101 (34.0)
CAF or CMF	353 (49.3)	115 (52.8)	143 (48.1)
Other chemotherapy agents	150 (20.9)	31 (14.2)	53 (17.8)
Method of detection[a]			
Screening mammogram	61 (9.8)	28 (14.5)	31 (11.2)
Clinical breast exam	57 (9.1)	20 (10.4)	30 (10.8)
Self-detected	505 (81.1)	145 (75.1)	216 (78.0)

[a]As reported by subject or proxy in follow-up interview.

group for almost all other tumor features, although these associations were within the limits of chance.

Last, we considered the risk of dying in relation to family history in conjunction with established tumor features (Table 6). The presence of a first-degree family history of breast cancer was associated with a significant reduction in the risk of dying (HR: 0.7; 95% CI: 0.5–0.9) independent of the prognostic effects of age, year of diagnosis, tumor size, nodal status, grade, and ER/PR/HER2 status. Results were similar upon exclusion of *BRCA1*/*BRCA2* mutation carriers.

Discussion

Our results indicate that women diagnosed with invasive breast cancer at a young age who have features of inherited predisposition, including a mother or sister with breast cancer, one or more relatives with breast cancer diagnosed at an early age, and/or multiple affected relatives do not have an increased risk of dying and in fact, have a substantively reduced risk of dying when compared with breast cancer cases with a negative family history of breast cancer. This study was unique in its focus

Table 3. Relative risk of dying in relation to family history characteristics among 1,260 nonadopted women diagnosed with invasive breast cancer in 1983 to 1992 at age 45 or younger

Characteristic	Alive *N* = 833 *N* (%)	Deceased *N* = 427 *N* (%)	All women *N* = 1,260 HR[a] (95% CI)	Excluding *BRCA1/2* + women *N* = 1,225 HR[a,b] (95% CI)
Family history of breast cancer[c]				
None	462 (63.9)	261 (36.1)	1.0 (Ref.)	1.0 (Ref.)
First-degree	165 (74.3)	57 (25.7)	0.6 (0.5–0.8)	0.7 (0.5–0.9)
Second-degree only	195 (65.0)	105 (35.0)	0.9 (0.8–1.2)	1.0 (0.8–1.2)
Relative (first- or second degree) diagnosed with breast cancer less than age 45[c]				
No affected relatives	462 (63.9)	261 (36.1)	1.0 (Ref.)	1.0 (Ref.)
1+ relatives diagnosed age <45	107 (71.8)	42 (28.2)	0.7 (0.5–0.9)	0.7 (0.5–1.0)
All diagnosed age 45+	224 (69.1)	100 (30.9)	0.8 (0.7–1.0)	0.8 (0.7–1.0)
1+ First-degree relatives diagnosed age <45	70 (76.1)	22 (23.9)	0.6 (0.4–0.9)	0.6 (0.4–1.0)[d]
All first-degree relatives diagnosed age 45+	90 (73.8)	32 (26.2)	0.7 (0.5–1.0)[d]	0.7 (0.5–1.0)[d]
Number of relatives with breast cancer[c]				
No affected relatives	462 (63.9)	261 (36.1)	1.0 (Ref.)	1.0 (Ref.)
1 First/second-degree relatives affected	233 (66.6)	117 (33.4)	0.9 (0.7–1.1)	0.9 (0.7–1.1)
2 First/second-degree relatives affected	83 (73.5)	30 (26.5)	0.7 (0.5–1.0)[d]	0.7 (0.5–1.0)[d]
3+ First/second-degree relatives affected	44 (74.6)	15 (25.4)	0.6 (0.3–1.0)[d]	0.7 (0.4–1.2)
P_{trend}			0.05	0.12
1 First degree affected	141 (72.7)	53 (27.3)	0.7 (0.5–0.9)	0.7 (0.5–1.0)[d]
2+ First-degree relatives affected	24 (85.7)	4 (14.3)	0.3 (0.1–0.8)	0.3 (0.1–0.9)
1 Second-degree relatives affected	205 (67.0)	101 (33.0)	0.9 (0.7–1.1)	0.9 (0.7–1.1)
2 Second-degree relatives affected	50 (71.4)	20 (28.6)	0.7 (0.4–1.1)	0.8 (0.5–1.2)
3+ Second-degree relatives affected	15 (65.2)	8 (34.8)	0.8 (0.4–1.7)	0.9 (0.4–1.8)
P_{trend}			0.42	0.65

[a]HRs adjusted for age (continuous) and year (exact) of diagnosis.
[b]Thirty-five women with mutation in *BRCA1/2* are excluded.
[c]Fifteen women with at least one first-degree relative with unknown breast cancer status were excluded
[d]CI excludes 1.0.

on women diagnosed with breast cancer at a young age, and most past studies of family history and survival have had insufficient power to focus on young women, in which mortality rates are so high. In turn, it is worth noting that the results of this study are not necessarily generalizable to women diagnosed with breast cancer at older ages.

The survival advantage afforded in this study for cases with first-degree family history is compatible with findings of improved survival in a number of prior studies (1–5, 7), including our preliminary report on a portion of the cases in this analysis (6), but in contrast to findings in other studies of worse survival (16–18), and no difference (9, 10, 12, 13, 15, 39), although these past studies largely had limited numbers of young women. Only 4 studies reported on young cases, one finding somewhat worse survival (14), 2 finding improved survival (7, 8), and another finding no association (15) between family history and survival, but only one of these studies excluded *BRCA1*/*BRCA1* carriers and another was exceedingly small in sample size. Past studies have varied in their definitions of positive family history. We examined family history in a number of ways, including by the presence of breast cancer in any first- versus only second-degree relatives, age of diagnosis in relatives, numbers of affected relatives, and individual relative type, and found considerable consistency in the observation of a reduced risk of death in relation to first-degree family history and multiple affected relatives. One recent report of a nonstatistically significant reduction in the risk of dying related to first-degree family history of breast or ovarian cancer (HR: 0.86; 95% CI: 0.71–1.05) noted a further improvement in survival for those with multiple affected first-degree relatives (HR: 0.21; 95% CI: 0.03–1.49), but this was based on limited follow-up and only one death in those with multiple affected relatives (8).

The infrequent nature of *BRCA1*/*BRCA2* mutations, even in women with a first-degree family history

Table 4. Relative risk of dying in relation to family history of breast cancer according to clinical characteristics and treatment among 1,260 nonadopted women diagnosed with invasive breast cancer in 1983 to 1992 at age 45 or younger

	No family history	First-degree family history	Second-degree family history	
	HR[a]	HR[a] (95% CI)	HR[a] (95% CI)	$P_{interaction}$
Age of diagnosis				
<35 years	1.0	0.6 (0.3–1.1)	1.2 (0.8–1.8)	0.40
35+ years	1.0	0.6 (0.5–0.9)	0.9 (0.7–1.1)	
Year of diagnosis				
1983–1986	1.0	0.5 (0.3–0.9)	1.0 (0.7–1.6)	0.45
1987–1992	1.0	0.7 (0.5–0.9)	0.9 (0.7–1.2)	
Source study				
First (1 of 83—4 to 90)	1.0	0.6 (0.4–0.9)	0.9 (0.7–1.2)	0.89
Second (5 of 90–12 of 92)	1.0	0.7 (0.4–1.1)	1.1 (0.7–1.5)	
Stage of disease (SEER stage)				
Local	1.0	0.8 (0.5–1.2)	1.0 (0.7–1.4)	0.51
Regional/distant	1.0	0.6 (0.4–0.9)	1.0 (0.8–1.4)	
Tumor size				
≤2 cm	1.0	0.6 (0.4–0.9)	1.0 (0.7–1.5)	0.47
>2–5 cm	1.0	0.8 (0.5–1.2)	0.9 (0.7–1.3)	
>5 cm	1.0	0.5 (0.1–1.5)	0.6 (0.3–1.2)	
Nodal status				
Negative	1.0	0.7 (0.5–1.2)	0.9 (0.7–1.4)	0.55
Positive	1.0	0.6 (0.4–0.9)	1.0 (0.8–1.4)	
Mammography history				
No prior mammograms	1.0	0.7 (0.5–1.1)	1.1 (0.8–1.5)	0.32
Yes prior mammograms	1.0	0.6 (0.4–0.9)	0.8 (0.5–1.1)	
Method of detection[c]				
Screening mammogram	1.0	0.7 (0.2–2.1)	0.8 (0.3–2.3)	0.61
Clinical breast exam	1.0	0.5 (0.2–1.5)	1.3 (0.6–2.6)	
Self-detected	1.0	0.7 (0.5–1.0)[d]	1.0 (0.8–1.3)	
Radiation[b]				
No	1.0	0.7 (0.5–1.1)	1.0 (0.7–1.4)	0.96
Yes	1.0	0.6 (0.4–0.9)	1.0 (0.7–1.3)	
Chemotherapy[b]				
No	1.0	0.7 (0.4–1.2)	1.2 (0.8–1.8)	0.39
Yes	1.0	0.7 (0.5–1.0)[d]	0.9 (0.7–1.2)	

[a]HRs adjusted for age at diagnosis (continuous) and year of diagnosis (exact).
[b]HRs adjusted for age at diagnosis (continuous), year of diagnosis (exact), and stage (SEER).
[c]As reported by subject or proxy in follow-up interview.
[d]CI excludes 1.0.

(35, 40), suggests they likely do not play a major role in any association between family history and survival. A strength of this study was the ability to assess to what extent, if any, an effect of family history on survival was attributable to *BRCA1*/*BRCA2*. We genotyped the majority of cases with a first-degree family history (172 of 222) and results were unchanged when we included or excluded mutation carriers.

A primary goal of this study was to consider whether associations between family history and survival might be explained by differences in factors such as mammographic screening, method of cancer detection, and treatment on the premise that these factors could vary by family history. Although cases with a first-degree family history more often had smaller tumors and cases with either a first- or second-degree family history more often had had a prior mammogram, neither factor seemed to account for the observed reduction in mortality. Similarly, there was no evidence that treatment modified the association between family history and mortality, nor does the improved survival we observed seem to be attributable to other potential confounders.

Table 5. Relationship of family history of breast cancer to histopathology and tumor markers[a,b]

	No family history $N = 716$	First degree family history $N = 198$		Second degree family history $N = 296$	
Tumor characteristic	***N* (%)**	***N* (%)**	**OR[c] (95% CI)**	***N* (%)**	**OR[c] (95% CI)**
Stage of disease (SEER stage)					
Local	390 (55.1)	120 (61.5)	1.0 (Ref.)	181 (61.6)	1.0 (Ref.)
Regional	300 (42.4)	72 (36.9)	0.8 (0.6–1.1)	110 (37.4)	0.8 (0.6–1.0)
Distant	18 (2.5)	3 (1.5)	0.6 (0.2–2.0)	3 (1.0)	0.4 (0.1–1.3)
Tumor size (cm)					
≤2	356 (50.8)	114 (58.5)	1.0 (Ref.)	148 (51.6)	1.0 (Ref.)
>2–5	283 (40.4)	73 (37.4)	0.8 (0.6–1.1)	111 (38.7)	0.9 (0.7–1.3)
>5	62 (8.8)	8 (4.1)	0.4 (0.2–0.9)	28 (9.8)	1.1 (0.7–1.8)
Nodal status					
Negative	398 (56.5)	119 (60.7)	1.0 (Ref.)	182 (62.5)	1.0 (Ref.)
1 Positive node	77 (10.9)	20 910.2)	0.9 (0.5–1.5)	28 (9.6)	0.8 (0.5–1.3)
2 Positive node	38 (5.4)	7 (3.6)	0.6 (0.3–1.5)	21 (7.2)	1.2 (0.7–2.2)
3+ Positive node	121 (17.2)	24 (12.2)	0.7 (0.4–1.1)	31 (10.7)	0.6 (0.4–0.9)
Unknown # positive node	71 (10.1)	26 (13.3)	1.2 (0.7–1.9)	29 (10.0)	0.9 (0.5–1.4)
Histology					
Ductal	585 (81.7)	165 (83.3)	1.0 (Ref.)	253 (85.5)	1.0 (Ref.)
Lobular	39 (5.4)	10 (5.1)	0.9 (0.4–1.9)	12 (4.1)	0.7 (0.4–1.4)
Other	92 (12.8)	23 (11.6)	0.9 (0.5–1.4)	31 (10.5)	0.8 (0.5–1.2)
Histologic grade					
Low	102 (18.6)	36 (25.0)	1.0 (Ref.)	43 918.5)	1.0 (Ref.)
Intermediate	208 (37.9)	51 (35.4)	0.7 (0.4–1.1)	79 (34.1)	0.9 (0.6–1.4)
High	239 (43.5)	57 (39.6)	0.7 (0.4–1.1)	110 (47.4)	1.1 (0.7–1.7)
Nuclear grade[d]					
Low/intermediate	299 (52.5)	88 (57.9)	1.0 (Ref.)	124 (52.1)	1.0 (Ref.)
High	270 (47.5)	64 (42.1)	0.8 (0.5–1.1)	114 (47.9)	1.0 (0.7–1.4)
Mitotic count[d]					
Low	213 (38.8)	62 (43.1)	1.0 (Ref.)	85 (36.6)	1.0 (Ref.)
Intermediate	170 (31.0)	43 (29.9)	0.9 (0.6–1.4)	74 (31.9)	1.1 (0.5–1.8)
High	166 (30.2)	39 (27.1)	0.8 (0.5–1.3)	73 (31.5)	1.1 (0.8–1.6)
Differentiation[d]					
Low	46 (8.4)	19 (13.2)	1.0 (Ref.)	18 (7.8)	1.0 (Ref.)
Intermediate	119 (21.7)	31 (21.5)	0.6 (0.3–1.2)	44 (19.0)	1.0 (0.5–1.8)
High	384 (69.9)	94 (65.3)	0.6 (0.3–1.0)	170 (73.3)	1.1 (0.6–2.0)
Estrogen receptor					
Positive	298 (58.4)	90 (66.7)	1.0 (Ref.)	121 (58.7)	1.0 (Ref.)
Negative	212 (41.6)	45 (33.3)	0.7 (0.5–1.0)	85 (41.3)	1.0 (0.7–1.4)
Progesterone receptor					
Positive	310 (60.8)	86 (64.2)	1.0 (Ref.)	122 (59.5)	1.0 (Ref.)
Negative	200 (39.2)	48 (35.8)	0.8 (0.6–1.2)	83 (40.5)	1.0 (0.7–1.5)
Cyclin E					
Low	386 (75.4)	105 (77.8)	1.0 (Ref.)	156 (75.4)	1.0 (Ref.)
High	126 (24.6)	30 (22.2)	0.9 (0.5–1.4)	51 (24.6)	1.0 (0.7–1.5)
BCL-2					
High	206 (40.8)	66 (48.9)	1.0 (Ref.)	86 (42.2)	1.0 (Ref.)
Low	299 (59.2)	69 (51.1)	0.7 (0.5–1.1)	118 (57.8)	0.9 (0.7–1.3)
p53					
Negative	297 (58.1)	86 (63.7)	1.0 (Ref.)	126 (61.2)	1.0 (Ref.)
Positive	214 (41.9)	49 (36.3)	0.8 (0.5–1.2)	80 (38.8)	0.9 (0.6–1.2)

(Continued on the following page)

Table 5. Relationship of family history of breast cancer to histopathology and tumor markers[a,b] (Cont'd)

	No family history $N = 716$	First degree family history $N = 198$		Second degree family history $N = 296$	
Tumor characteristic	***N* (%)**	***N* (%)**	**OR[c] (95% CI)**	***N* (%)**	**OR[c] (95% CI)**
p27					
Intermediate/high	267 (52.8)	74 (54.8)	1.0 (Ref.)	104 (50.7)	1.0 (Ref.)
Low	239 (47.2)	61 (45.2)	0.9 (0.6–1.3)	101 (49.3)	1.1 (0.8–1.5)
HER2					
Negative	342 (66.9)	95 (71.4)	1.0 (Ref.)	133 (64.3)	1.0 (Ref.)
Positive	169 (33.1)	38 (28.6)	0.8 (0.5–1.2)	74 (35.7)	1.1 (0.8–1.6)
Ki-67 (average ratio)					
0%–24%	307 (60.4)	81 (60.4)	1.0 (Ref.)	124 (60.8)	1.0 (Ref.)
25%–100%	201 (39.6)	53 (39.6)	1.0 (0.7–1.5)	80 (39.2)	1.0 (0.7–1.4)

[a]Thirty-five women with either a *BRCA1* or *BRCA2* mutation are excluded.

[b]Total for these variables varies. Although stage, tumor size, and nodal status are available for most women from the cancer registry and/or medical record review, data on the remaining factors are limited to women whose tissue was available for centralized review and/or testing).

[c]ORs adjusted for age (continuous) and year (exact) of diagnosis.

[d]These tumor characteristics are constituents of histologic grade.

Few studies have considered tumor characteristics in relation to family history and those that have were confined largely to basic features such as nodal status and tumor size. In our study, women with a first-degree family history had tumors with a generally more favorable prognostic profile as assessed by nodal status and size. Smaller tumor sizes and/or less advanced stage for family history–positive cases has been reported in some (1, 5, 39, 41, 42) but not other (2, 4, 10, 12, 14) prior studies. Although past studies have not reported on mammography, a hospital-based study of 2,256 breast cancers found that not only family history–positive tumors were smaller but also that they were more likely to be detected without symptoms, consistent with the heightened proportion with prior mammography histories we observed (42). Despite finding that first-degree family history–positive cases had smaller tumors, the association between family history and the risk of dying did not vary nor was confounded by stage, nodal status, or size.

Compared with women with no family history, the tumors of women in our study with a first-degree family history were more likely to be ER positive and less differentiated. The propensity for *BRCA1* (but not *BRCA2*) mutation carriers to have ER-negative tumors is well established (43, 44). Our tumor analyses exclude most of the expected mutation carriers and thus our finding on ER is broadly compatible with previous findings among noncarriers of *BRCA1*/*BRCA2* mutations with a positive family history (45). A few prior studies have examined ER and reported little or no difference according to family history, but these studies were not focused on young women in which the proportion of ER-negative tumors is much greater (5, 12, 39). Molino and colleagues found that cases with a positive family history were more likely to have ER-positive tumors but this study included few younger women (42). Another recent report in women of all ages found no association between family history and tumor classified by ER, PR, and HER2 (28). In our study, the tumors of women with a first-degree family history had more favorable (though not statistically different) profiles with regard to a number of other prognostic features, including grade and expression of PR, BCL-2, p53, and HER2. Women with only a second-degree family history had tumor profiles that more closely resembled women with no family history.

Strengths of this study include its population-based design, large sample size, and centralized pathology review and tumor analysis. The follow-up period was extensive and longer than most past studies, reducing concern that observed relationships are a short-term phenomenon. Our findings are strengthened by the ability to assess the potential confounding effects of mammographic screening, the method of cancer detection, and treatment regimens.

Our findings must be considered in light of potential limitations. A population-based study offers broader generalizability to the wide spectrum of family histories in the general population and especially for the modest to minimal family histories usually seen outside of high-risk clinics. However, generalizability may be tempered by the extent to which the 15% of women otherwise eligible for the study who never participated (a group which experienced greater 5-year mortality) differ from participants in terms of the association between family history and mortality. Similar to most studies, we relied on self-reported family histories; however, multiple validation studies indicate that self-reported family histories of breast cancer are largely accurate (46–49). Interpretability

Table 6. Multivariate model of family history in relation to the risk of dying

Characteristic	Alive $N = 833$ *n* (%)	Dead $N = 427$ *n* (%)	All women $N = 1{,}260$ HR[b] (95% CI)	Excluding *BRCA1/2* carriers[a] $N = 1{,}225$ HR[b] (95% CI)
Family history of breast cancer				
None	462 (63.9)	261 (36.1)	1.0 (Ref.)	1.0 (Ref.)
First degree	165 (74.3)	57 (25.7)	0.7 (0.5–0.9)	0.7 (0.5–1.0)[d]
Second degree only	195 (65.0)	105 (35.0)	1.0 (0.8–1.3)	1.1 (0.8–1.3)
Unknown first degree	11	4		
Tumor size (cm)				
≤2	482 (75.0)	161 (25.0)	1.0 (Ref.)	1.0 (Ref.)
>2–5	288 (59.3)	198 (40.7)	1.3 (1.1–1.7)	1.3 (1.1–1.7)
>5	46 (45.5)	55 (54.5)	1.8 (1.3–2.4)	1.7 (1.2–2.4)
Missing	17	13		
Nodal status				
Negative	560 (76.9)	168 (23.1)	1.0 (Ref.)	1.0 (Ref.)
1 Pos node	89 (67.4)	43 (32.6)	1.4 (1.0–2.0)[d]	1.5 (1.0–2.1)[d]
2 Pos node	34 (50.7)	33 (49.3)	2.4 (1.6–3.5)	2.4 (1.6–3.6)
3+ Pos node	78 (42.6)	105 (57.4)	3.0 (2.3–3.9)	3.1 (2.4–4.1)
Unknown # Pos node	63 (52.3)	63 (47.7)	2.0 (1.4–2.8)	2.0 (1.4–2.8)
Missing	3	15		
Histologic grade[c]				
Low	148 (80.0)	37 (20.0)	1.0 (Ref.)	1.0 (Ref.)
Intermediate	216 (61.5)	135 (38.5)	1.6 (1.1–2.3)	1.6 (1.1–2.3)
High	264 (62.1)	161 (37.9)	1.5 (1.0–2.3)[d]	1.6 (1.0–2.3)[d]
Missing data	205 (68.6)	94 (31.4)	1.1 (0.7–1.7)	1.1 (0.7–1.7)
ER/PR/HER2[d]				
Pos/Pos/Neg	203 (70.2)	86 (29.8)	1.0 (Ref.)	1.0 (Ref.)
Pos/Neg/Neg	26 (46.4)	30 (53.6)	2.0 (1.3–3.1)	2.0 (1.3–3.1)
Pos/Pos/Pos	100 (65.4)	53 (34.6)	1.0 (0.7–1.4)	1.0 (0.7–1.4)
Pos/Neg/Pos	10 (45.5)	12 (54.5)	1.9 (1.0–3.7)[d]	1.9 (1.0–3.6)
Neg/Pos/Neg	49 (76.6)	15 (23.4)	0.5 (0.3–1.0)[d]	0.5 (0.3–1.0)[d]
Neg/Neg/Neg	126 (68.1)	59 (31.9)	0.9 (0.6–1.3)	0.9 (0.6–1.3)
Neg/Pos/Pos	14 (53.8)	1 (46.2)	1.6 (0.9–3.0)	1.6 (0.9–3.0)
Neg/Neg/Pos	46 (54.8)	38 (45.2)	1.6 (1.0–2.3)	1.6 (1.1–2.4)
Missing data	259 (68.0)	122 (32.0)	1.0 (0.7–1.4)	1.0 (0.7–1.4)

Abbreviations: Pos, positive; Neg, negative.

[a]Thirty-five women with either a *BRCA1* or *BRCA2* mutation are excluded.

[b]HRs adjusted for age (continuous) and year (exact) of diagnosis, and other variables in the table.

[c]Missing data for these 2 variables was included as a separate category in the model.

[d]CI excludes 1.0.

of studies of survival outside of a clinical trial can be hampered by the unavailability of treatment information and/or the nonrandomized nature of treatment. Our medical record review elicited extensive, comprehensive treatment detail and given the high proportion of reviews completed and the high proportion for which complete therapy information was obtained, it is unlikely that missing information accounts for these results. We saw no evidence that treatment modified or confounded results. Despite having information on mammography and the method of detection, our finding of a reduced risk of dying in women with a first-degree family history may nonetheless be, in part, attributable to unmeasured residual confounding involving behaviors associated with having a family history. This topic warrants further study.

There are also technical considerations for the laboratory analyses. *BRCA1/BRCA2* genotyping was carried out in the mid-1990s with SSCP (34–36). Although a widely accepted technology at the time, newer methods detect a higher proportion of mutations (50) and some mutations were likely missed. *BRCA1/BRCA2* genotyping was carried out on only 25.6% of the cohort, targeting subgroups most likely to carry a mutation. Prior studies, including our own in this population (34, 35) and others (51–53),

have shown relatively low mutation frequencies in women with a family history and/or an early age of diagnosis (<10%–12%) and considerably smaller carrier frequencies outside of these higher risk groups, thus, it is unlikely that many mutations were missed in the untested group. Tumor tissue for IHC analysis was unavailable for 29% of participants. Comparison of women IHC tested and not tested showed no differences in vital status, stage, tumor size, nodal status, and family history. Tissue availability varied slightly by age, in that women with unavailable specimens were younger than those with available tissue ($P < 0.01$). This is not unexpected because tissue unavailability was greater for the earliest diagnosis years, imposing disproportionate losses in years when a greater proportion of cases was very young (an artifact due to the birth year eligibility criteria in our first study) compared with later years when the age spectrum went up to age 44.

Our results point toward better survival for women diagnosed with breast cancer at a young age that have certain hallmarks of inherited predisposition, including first-degree family history of breast cancer and multiple affected relatives. Larger replication studies are needed. Because the vast majority of women with a first-degree family history do not carry mutations in *BRCA1*/*BRCA2*, these findings suggest that other shared genetic factors may contribute not only to an increased risk of developing breast cancer, but also possibly to distinctive tumor features and prognosis. To the extent that these associations are replicated and extended, they could be important in terms of prognostication and treatment strategies. The greatest benefit would come as mechanisms and specific pathways that may underlie disease progression among women with varying inherited predisposition profiles are identified.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The authors thank the study participants and area physicians for their generous contributions to this study and the many staff who completed the data collection activities.

Grant Support

This work was supported, in part, by grants and contracts R01-CA-63705, R01-CA-41416, N01-CP-95671, R01-CA-59736, and R21-CA-66186 from the National Cancer Institute.

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Received August 12, 2011; revised September 22, 2011; accepted September 23, 2011; published OnlineFirst September 28, 2011.

References

1. Langlands AO, Kerr GR, Bloomer SM. Familial breast cancer. Clin Oncol 1976;2:41–5.
2. Lynch HT, Albano WA, Recabaren JA, Fain PR, Lynch PM. Survival in hereditary breast and colon cancer. JAMA 1981;246:1197.
3. Albano WA, Recabaren JA, Lynch HT, Campbell AS, Mailliard JA, Organ CH, et al. Natural history of hereditary cancer of the breast and colon. Cancer 1982;50:360–3.
4. Wobbes T, vandeWiel MP, vanderSluis RF, Theeuwes AGM. The effect of familiality on clinical presentation and survival in mammary carcinoma. Eur J Surg Oncol 1987;13:119–21.
5. Fukutomi T, Kobayashi Y, Nanasawa T, Yamamoto H, Tsuda H. A clinicopathological analysis of breast cancer in patients with a family history. Surg Today 1993;23:849–54.
6. Malone KE, Daling JR, Weiss NS, McKnight B, White E, Voigt LF. Family history and survival of young women with invasive breast carcinoma. Cancer 1996;78:1417–25.
7. Mohammed SN, Smith P, Hodgson SV, Fentiman IS, Miles DW, Barnes DM, et al. Family history and survival in premenopausal breast cancer. Br J Cancer 1998;77:2252–6.
8. Thalib L, Wedren S, Granath F, Adami HO, Rydh B, Magnusson C, et al. Breast cancer prognosis in relation to family history of breast and ovarian cancer. Br J Cancer 2004;90:1378–81.
9. Greenberg ER, Vessey MP, McPherson K, Doll R, Yeates D. Body size and survival in premenopausal breast cancer. Br J Cancer 1985;51:691–7.
10. Anderson DE, Badzioch MD. Survival in familial breast cancer patients. Cancer 1986;58:360–5.
11. Ruder AM, Moodie PF, Nelson NA, Choi NW. Does family history of breast cancer improve survival among patients with breast cancer. Am J Obstet Gynecol 1988;158:963–8.
12. Israeli D, Tartter PI, Brower ST, Mizrachy B, Bratton J. The significance of family history for patients with carcinoma of the breast. J Am Coll Surg 1994;179:29–32.
13. Schouten LJ, Hupperets PS, Jager JJ, Volovics L, Wils JA, Verbeek AL, et al. Prognostic significance of etiological risk factors in early breast cancer. Breast Cancer Res Treat 1997;43:217–23.
14. Russo A, Herd-Smith A, Gestri D, Bianchi S, Vezzosi V, Rosselli Del TM, et al. Does family history influence survival in breast cancer cases?Int J Cancer 2002;99:427–30.
15. Chang ET, Milne RL, Phillips KA, Figueiredo JC, Sangaramoorthy M, Keegan TH, et al. Family history of breast cancer and all-cause mortality after breast cancer diagnosis in the Breast Cancer Family Registry. Breast Cancer Res Treat 2009;117:167–76.
16. Lees AW, Jenkins HJ, May CL, Cherian G, Lam EW, Hanson J. Risk factors and 10-year breast cancer survival in northern Alberta. Breast Cancer Res Treat 1989;13:143–51.
17. Chen LM, Mundt AJ, Power C, Halpern HJ, Weichselbaum RR. Significance of family history in breast cancer treated with breast conservation therapy. Breast J 1996;2:245.
18. Slattery ML, Berry TD, Kerber RA. Is survival among women diagnosed with breast cancer influenced by family history of breast cancer? Epidemiology 1993;4:543–8.
19. Verkooijen HM, Rapiti E, Fioretta G, Vinh-Hung V, Keller J, Benhamou S, et al. Impact of a positive family history on diagnosis, management, and survival of breast cancer: different effects across socio-economic groups. Cancer Causes Control 2009;20:1689–96.
20. Porter DE, Cohen BB, Wallace MR, Smyth E, Chetty U, Dixon JM, et al. Breast cancer incidence, penetrance and survival in probable carriers of BRCA1 gene mutation in families linked to BRCA1 on chromosome 17q12-21. Br J Surg 1994;81:1512–5.
21. Marcus JN, Watson P, Page DL, Narod SA, Lenoir GM, Tonin P, et al. Hereditary breast cancer: pathobiology, prognosis, and BRCA1 and BRCA2 gene linkage. Cancer 1996;77:697–709.
22. Verhoog LC, Brekelmans CT, Seynaeve C, van den Bosch LM, Dahmen G, van Geel AN, et al. Survival and tumour characteristics of

breast-cancer patients with germline mutations of BRCA1. Lancet 1998;351:316–21.
23. Lee JS, Wacholder S, Struewing JP, McAdams M, Pee D, Brody LC, et al. Survival after breast cancer in Ashkenazi Jewish BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 1999;91:259–63.
24. Johannsson OT, Ranstam J, Borg A, Olsson H. Survival of BRCA1 breast and ovarian cancer patients: a population-based study from southern Sweden. J Clin Oncol 1998;16:397–404.
25. Foulkes WD, Wong N, Brunet JS, Narod SA. BRCA mutations and survival in breast cancer. J Clin Oncol 1998;16:3206–8.
26. Foulkes WD, Chappuis PO, Wong N, Brunet JS, Vesprini D, Rozen F, et al. Primary node negative breast cancer in BRCA1 mutation carriers has a poor outcome. Ann Oncol 2000;11:307–13.
27. Stoppa-Lyonnet D, Ansquer Y, Dreyfus H, Gautier C, Gauthier-Villars M, Bourstyn E, et al. Familial invasive breast cancers: worse outcome related to BRCA1 mutations. J Clin Oncol 2000;18:4053–9.
28. Yang XR, Chang-Claude J, Goode EL, Couch FJ, Nevanlinna H, Milne RL, et al. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the breast cancer association consortium studies. J Natl Cancer Inst 2011;103:250–63.
29. Chappuis PO, Rosenblatt J, Foulkes WD. The influence of familial and hereditary factors on the prognosis of breast cancer. Ann Oncol 1999;10:1163–70.
30. Hankey BF, Ries LA, Edwards BK. The surveillance, epidemiology, and end results program: a national resource. Cancer Epidemiol Biomarkers Prev 1999;8:1117–21.
31. Daling JR, Malone KE, Voigt LF, White E, Weiss NS. Risk of breast cancer among young women: relationship to induced abortion. J Natl Cancer Inst 1994;86:1584–92.
32. Brinton LA, Daling JR, Liff JM, Schoenberg JB, Malone KE, Stanford JL, et al. Oral contraceptives and breast cancer risk among younger women. J Natl Cancer Inst 1995;87:827–35.
33. Daling JR, Malone KE, Doody DR, Anderson BO, Porter PL. The relation of reproductive factors to mortality from breast cancer. Cancer Epidemiol Biomarkers Prev 2002;11:235–41.
34. Malone KE, Daling JR, Thompson JD, O'Brien CA, Francisco LV, Ostrander EA. BRCA1 mutations and breast cancer in the general population: analyses in women before age 35 years and in women before age 45 years with first-degree family history. JAMA 1998;279:922–9.
35. Malone KE, Daling JR, Neal C, Suter NM, O'Brien C, Cushing-Haugen K, et al. Frequency of BRCA1/BRCA2 mutations in a population-based sample of young breast carcinoma cases. Cancer 2000;88:1393–402.
36. Langston AA, Malone KE, Thompson JD, Daling JR, Ostrander EA. BRCA1 mutations in a population-based sample of young women with breast cancer. N Engl J Med 1996;334:137–42.
37. Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. New York: Springer; 1997.
38. Daling JR, Malone KE, Doody DR, Johnson LG, Gralow JR, Porter PL. Relation of body mass index to tumor markers and survival among young women with invasive ductal breast carcinoma. Cancer 2001;92:720–9.
39. Haas JA, Schultz DJ, Peterson ME, Solin LJ. An analysis of age and family history on outcome after breast-conservation treatment: the University of Pennsylvania experience. Cancer J Sci Am 1998;4:308–15.
40. Loman N, Bladstrom A, Johannsson O, Borg A, Olsson H. Cancer incidence in relatives of a population-based set of cases of early-onset breast cancer with a known BRCA1 and BRCA2 mutation status. Breast Cancer Res 2003;5:175–86.
41. Colditz GA, Willett WC, Hunter DJ, Stampfer MJ, Manson JE, Hennekens CH, et al. Family history, age, and risk of breast cancer. Prospective data from the Nurses' Health Study. JAMA 1993;270:338–43.
42. Molino A, Giovannini M, Pedersini R, Frisinghelli M, Micciolo R, Mandara M, et al. Correlations between family history and cancer characteristics in 2256 breast cancer patients. Br J Cancer 2004;91:96–8.
43. Armes JE, Trute L, White D, Southey MC, Hammet F, Tesoriero A, et al. Distinct molecular pathogeneses of early-onset breast cancers in BRCA1 and BRCA2 mutation carriers: a population-based study. Cancer Res 1999;59:2011–7.
44. Phillips KA. Immunophenotypic and pathologic differences between BRCA1 and BRCA2 hereditary breast cancers. J Clin Oncol 2000;18:107S–12S.
45. Loman N, Johannsson O, Bendahl PO, Borg A, Ferno M, Olsson H. Steroid receptors in hereditary breast carcinomas associated with BRCA1 or BRCA2 mutations or unknown susceptibility genes. Cancer 1998;83:310–9.
46. Love RR, Evans AM, Josten DM. The accuracy of patient reports of a family history of cancer. J Chronic Dis 1985;38:289–93.
47. Theis B, Boyd N, Lockwood G, Tritchler D. Accuracy of family cancer history in breast cancer patients. Eur J Cancer Prev 1994;3:321–7.
48. Parent ME, Ghadirian P, Lacroix A, Perret C. Accuracy of reports of familial breast cancer in a case-control series. Epidemiol 1995;6:184–6.
49. Novakovic B, Goldstein AM, Tucker MA. Validation of family history of cancer in deceased family members. J Natl Cancer Inst 1996;88:1492–3.
50. Eng C, Brody LC, Wagner TM, Devilee P, Vijg J, Szabo C, et al. Interpreting epidemiological research: blinded comparison of methods used to estimate the prevalence of inherited mutations in BRCA1. J Med Genet 2001;38:824–33.
51. Loman N, Johannsson O, Kristoffersson U, Olsson H, Borg A. Family history of breast and ovarian cancers and BRCA1 and BRCA2 mutations in a population-based series of early-onset breast cancer. J Natl Cancer Inst 2001;93:1215–23.
52. Newman B, Mu H, Butler LM, Millikan RC, Moorman PG, King MC. Frequency of breast cancer attributable to BRCA1 in a population-based series of American women. JAMA 1998;279:915–21.
53. Peto J, Collins N, Barfoot R, Seal S, Warren W, Rahman N, et al. Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. J Natl Cancer Inst 1999;91:943–9.