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# Population-based estimates of the relation between breast cancer risk, tumor subtype, and family history

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## Abstract

**Objective—**Many studies that have estimated the breast cancer risk attributable to family history have been based on data collected within family units. Use of this study design has likely overestimated risks for the general population. We provide population-based estimates of breast cancer risk and different tumor subtypes in relation to the degree, number, and age at diagnosis of affected relatives.

**Methods—**Cox Proportional Hazards to calculate risks (hazard ratios; 95% confidence interval) of breast cancer and tumor subtypes for women with a family history of breast cancer relative to women without a family history among a cohort of 75,189 women age ≥40 years of whom 1,087 were diagnosed with breast cancer from June 1, 2001-December 31, 2005 (median follow-up 3.16 years).

**Results—**Breast cancer risk was highest for women with a first-degree family history (1.54; 1.34-1.77); and did not differ substantially by the affected relative's age at diagnosis or by number of affected first-degree relatives. A second-degree family history only was not associated with a significantly increased breast cancer risk (1.15; 0.98-1.35). There was a suggestion that a positive family history was associated with risk of triple positive (Estrogen+/Progesterone+/HER2+) and HER2-overexpressing tumors.

**Conclusions—**While a family history of breast cancer in first-degree relatives is an important risk factor for breast cancer, gathering information such as the age at diagnosis of affected relatives or information on second-degree relative history may be unnecessary in assessing personal breast cancer risk among women age ≥40 years.

### Keywords

Breast cancer risk; family history; population-based; tumor subtype

## Introduction

A family history of breast cancer has long been considered an important risk factor for breast cancer. Research indicates that women with an affected first-degree relative (mother/father/

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sister/brother/daughter/son) or with any affected family member diagnosed <50 years have particularly high risks [1-7]. These associations may reflect a combination of factors, including high-penetrance inherited genetic mutations in genes such as BRCA1 and BRCA2, low-penetrance inherited mutations in genes such as GSTP1, and a shared family environment [8].

Estimates of the amount of increased breast cancer risk attributable to family history have varied by study design, population, and sample size [6]. Analyses of family-based studies, which systematically identify cases (probands) within families, may lead to inflated risk estimates since families under study may have unmeasured risk factors and/or high-risk genetic mutations [9]. Risk estimates obtained from population-based studies should be more robust and generalizable than risk estimates from family-based studies.

Population-based data from around the world has been comprehensively evaluated in a meta-analysis using data from 52 case-control and 22 cohort studies. Based on this analysis, women with a first-degree family history of breast cancer had a 2.1-fold (95% confidence interval (CI): 2.0–2.2) increased risk of breast cancer and women with a second-degree family history had a 1.5-fold (95%CI: 1.4–1.6) increased risk compared to women with no family history of breast cancer [6]. This meta-analysis was unable to explore the risks associated with having both a first and second-degree family history or having different numbers of affected family members of varying degrees. This meta-analysis also did not adjust for a woman's total number of relatives (affected and unaffected) or mammographic breast density.

Family history of breast cancer may be predictive of additional risk factors for breast cancer, such as breast density [10], and may predispose women to particular types of breast cancer, specifically breast tumors not over-expressing (-) estrogen and progesterone hormone receptors (ER/PR) or over-expressing (+) the proto-oncogene HER2-neu (HER2) [11-15]. Studies examining the relation between family history and ER/PR status have generally found no association, but have been limited by their sample sizes [16], and only one has evaluated the relation between family history and ER, PR, and HER2 status [15]. Identifying risk factors for molecular subtypes of breast cancer with particularity poor prognoses, HER2 over-expressing (ER−/PR−/HER2+) and basal type (ER−/PR−/HER2−) breast cancers [17-18], is important since risk factor data are currently lacking.

We studied the association between a woman's family history of breast cancer and her breast cancer risk in a population-based setting. We were able to take into account precise kinship of affected relatives (i.e., mother, sister, grandmother, aunt), degree of relationship of affected relatives (i.e., first or second), total number of relatives by degree, and whether relatives were diagnosed with breast cancer before age 50.

## Methods

### Study Subjects and Setting

This study was conducted among members of Group Health, a large integrated health plan in Western Washington State. Since 1986, women aged ≥40 years have been invited to enroll in a breast cancer screening program, which involves automated recruitment and reminder letters for women to initiate screening mammography [19-20]. As part of the screening program, women fill out a breast cancer risk factor questionnaire including detailed family history information. The questionnaire does not assess the maternal or paternal lineage of potentially affected aunts and grandmothers.

The questionnaire has two modes of administration: mailed and in-clinic. Women receive mailed questionnaires when they turn 40 years of age or upon enrollment in the health plan (if

≥40 years). Women also fill out risk factor questionnaires at each mammogram. Based on the information provided on these questionnaires, each woman receives reminders to get screening mammograms on risk-based screening intervals [19-20]. During this study, all women ≥50 years, and women between 40 and 49 years who were nulliparous, had an affected first or second-degree relative, menarche <11 years, were aged >30 years at first birth, or had a previous negative breast biopsy, received reminders for screening every two years. All other women <50 years were not recommended for routine screening mammography, but could still receive annual mammography. During this same time, all women ≥40 years with ≥2 affected first-degree relatives or atypical hyperplasia on a previous breast biopsy were reminded for screening annually [21-22].

All women aged ≥40 years that completed a questionnaire between 6/1/2001-12/31/2005, were eligible for inclusion in this study (N = 94,891). We excluded women from the analyses for the following reasons: reported "unknown" family history of breast cancer for all relatives (n=10,166), family history portion of the questionnaire was not completed (n=2,853), prior diagnosis of breast cancer (N=4,477), adopted and did not know the family history of their biological relatives (n=1,875), did not consent to have their data used for research (n=187), or had a previous unilateral or bilateral mastectomy (n=164).

All women entered the study on the date of their first completed questionnaire after June 1, 2001 and were followed until the first of the following: 1) breast cancer diagnosis (event), 2) disenrollment from Group Health (censored), 3) death (censored), or 4) end of follow-up (censored at end of study period December 31, 2005). The Group Health Institutional Review Board approved all analyses and data collection for this study.

## Breast Cancer Data

We identified all invasive and *in situ* breast cancer diagnoses in the cohort by linking records from the Western Washington Surveillance Epidemiology and End Results Reporting (SEER) registry. We used SEER data to characterize the tumors including ER and PR status, stage at diagnosis, tumor size, and lymph node involvement. HER2 over-expression status was abstracted from medical records at Group Health for a subgroup of women (44.3% of total, N=482).

## Family History Definitions

Women were considered to have a positive family history of breast cancer if they reported they had a mother, sister, aunt, or grandmother diagnosed with breast cancer. Affected fathers, brothers, and daughters were not included in our definition of a positive family history and analyses due to sample size. These specific relatives were also excluded from contributing to a woman's total number of relatives, both unaffected and affected, in all analyses. Family history exposures are described in detail in Appendix A. In all analyses, women with no reported breast cancer family history were the referent group. We examined risk associated with the following exposures: 1) First-degree family history a) alone and in combination with second degree family history; b) by number of relatives, and c) by age at diagnosis of affected relatives; 2) Second-degree family history a) alone; b) by number of relatives, and c) by age at diagnosis of affected relatives; and 3) Specific relative history a) by number of specific relatives, and b) by age of diagnosis of specific relatives. Analyses involving the number of affected sisters and aunts included only subjects with ≥1 sister or aunt.

## Statistical Analysis

We used Cox Proportional Hazards models to estimate hazard ratios (HR) and 95% CIs for the association between family history and subsequent risk of a breast cancer diagnosis [23]. We explored potential associations between family history of breast cancer and risk of having an

ER+/PR+, ER+/PR−, or ER−/PR− tumor among women with known ER and PR receptor status (N=858); we excluded women with ER−/PR+ tumors from this analysis due to the rarity of this subtype (N=11). We also explored the risk of having a Luminal A (ER+ and/or PR+ and HER2+), Luminal B (ER+ and/or PR+ and HER2−), HER2 over-expressing (ER−, PR−, and HER2+), or basal-type tumor (ER−, PR−, and HER2−) among women with available data for ER, PR, and HER2 status (N= 482) [24-25].

A list of potential confounders was determined *a priori* based on established breast cancer risk factors from the literature [8]. We explored potential confounding by age at baseline (quadratic), menopausal status (pre or peri-menopausal/post-menopausal), age at first birth (nulliparous/<30/≥30 years), benign breast biopsy history (yes/no), hormone therapy use (ever/never), age at menarche (<12/13/14/≥15), body mass index (BMI) (kg/m$^2$, continuous), breast density (almost entirely fat/scattered fibroglandular/heterogeneously dense/extremely dense) [26], and time since last mammogram (<3/≥3 years). For women with missing menopausal status information, we categorized women as post-menopausal if they were ≥55 years, reported prior use of hormone therapy, or reported a bilateral oophorectomy.

We also explored adjustment for each woman's total number of female relatives by using covariates that represented the total number (both unaffected and affected) of first-degree, second-degree, and specific types of female relatives that each woman reported. However, adjustment for these potential confounders and family size covariates did not notably alter risk estimates, so we only present age-adjusted risk estimates.

Women whose baseline risk information was obtained from a mailed questionnaire were more likely to be younger than age 50 (53.8% vs. 29.1%) and pre/peri-menopausal (48.0% vs. 29.6%) than were women whose baseline risk information was obtained from an in-clinic questionnaire. As a result, these women had substantially different crude baseline hazards for subsequent breast cancer diagnoses (202 and 523 events per 100,000 person-years, respectively). To account for these differences, all analyses were implicitly stratified by questionnaire source to allow the baseline hazards for these groups of women to differ [27]. We examined potential effect modification by questionnaire source, menopausal status, hormone therapy use and subject age (50/60/65/70/80 years) but found no statistically significant interactions.

All final models were examined for violations of the proportional hazards assumptions. No statistically significant deviations from proportional hazards were observed for standardized and non-standardized residuals on the time, log-time or rank scale. We examined pairwise comparisons to assess the difference between risk estimates across family history using Wald tests at a significance level of 0.05. All analyses were conducted in Stata SE, version 9.0 [28].

## Results

Among 75,169 women with a total of 218,424 person-years at risk, 1,087 women were diagnosed with breast cancer (Table 1). Relative to the entire cohort, women diagnosed with breast cancer were more likely to be older, postmenopausal, current users of estrogen and progestin hormone therapy, to have heterogeneously dense breasts, and to have a history of benign breast biopsy. Women diagnosed with breast cancer were also more likely to have had a screening or negative diagnostic mammogram in the three years before study entry (69.1% vs. 65.9%). The distributions of race, BMI, age at menarche, and age at first birth did not differ by breast cancer diagnosis.

In our cohort of 75,169 women with known family history, 19.5% (N=14,675) reported having a first-degree family history and 21.4% (N=16,073) reported having only a second-degree

family history (Table 2). Having a first-degree family history, with or without a second-degree family history, was associated with an increased breast cancer risk (HR=1.54; 95%CI: 1.34–1.77) compared to having no family history of breast cancer after adjusting for age of study subject at study entry. Neither the number of affected first-degree relatives nor the relative's age(s) at diagnosis substantially modified this risk (p-values 0.30 and 0.47, respectively). Women with second-degree family history only did not have a significantly higher risk of breast cancer than women with no family history (HR=1.15; 95%CI: 0.98–1.35), regardless of the number of affected second-degree relatives or their relative's age(s) at diagnosis. There was no significant difference in risk estimates when stratified by a woman's age at study entry.

Women whose mothers were diagnosed with breast cancer had a 56% higher risk of breast cancer than did women with no family history (95%CI: 1.31–1.86) (Table 3), with no significant difference in risk by maternal age of diagnosis (p-value = 0.96). The risk associated with having two affected grandmothers was significantly higher than the risk associated with having only one affected grandmother (p-value = 0.04). Among women with >1 sister or aunt, the risk among women with 1 affected sister/aunt was not significantly different than the risk among those with ≥2 affected sisters/aunts (p-values = 0.37 and 0.91, respectively) compared to women with no affected sisters/aunts.

After adjusting for age, women with a first-degree family history had increased risks of ER+/PR+ and ER+/PR− tumors, but not ER−/PR− tumors, compared to women with no family history (Table 4). Women with only a second-degree family history were not at an increased risk for any of the ER/PR tumor subtypes compared to women with no family history. Women with a first-degree family history experienced higher risks of Luminal A tumors compared to women with no family history (Table 5). There was also a suggestion that first-degree family history was related to risks of both Luminal B and HER2 over-expressing tumors (but not to risk of basal-type disease), though these risk estimates were within the limits of chance and are based on a small number of individuals.

## Discussion

In contrast to much of the published literature [2-3,6,29], our breast cancer risk estimates associated with family history of breast cancer assessed among women ≥40 years are uniformly lower in magnitude. Our results suggest that detailed collection of information on affected relative's age(s) at diagnosis and in second-degree relatives is not needed for disease free women ≥40. In our study, age at diagnosis of affected relatives did not significantly alter breast cancer risk and women with only a second-degree family history of breast cancer, in the absence of a first-degree history, were not at an increased risk for breast cancer. Although previous studies [1-2,5-7,29-30] suggest breast cancer risk is greater among women with first or second-degree relatives that have a younger age at diagnosis (i.e., <50 vs. ≥50 years), our estimates of these same risks were not significantly different from one another. Therefore our results may have important implications for streamlining the risk assessment of women ≥40 years during clinical care.

Our results suggest the ability to predict individuals with a high breast cancer risk would not be substantially improved by the collection of breast cancer history in second-degree relatives or the age at diagnosis of affected relatives. A simplified assessment of family history (i.e., only asking whether any mother, sister or aunt has been diagnosed with breast cancer) may adequately determine each woman's breast cancer risk attributable to family history once women have reached age 40. While detailed family history assessment may be crucial for certain diseases, our results suggest that detailed records of breast cancer history in second-degree relatives may be unnecessary, especially since the accuracy of self-reported second degree history may be questionable [31-32].

Worth noting is our finding that women who reported having two affected grandmothers experienced a significantly greater breast cancer risk than did women with only one affected grandmother, regardless of the grandmothers' age(s) at diagnosis. Although we did not gather information on lineage for the relatives in our study, the higher risk associated with having two affected grandmothers suggests the presence of disease in both maternal and paternal relatives is associated with a substantially increased risk. The notably different risk experienced by women with one versus two affected grandmothers suggests that collecting family history for these particular second-degree relatives may be important, although collecting age at diagnosis in grandmothers may be unnecessary. Additionally, having two or more affected relatives ≥50 years was associated with a greater risk of breast cancer than having one affected relative <50 years, albeit with wide confidence intervals around these estimates. Having two or more affected aunts may also reflect having a family history on both the maternal and paternal side thereby leading to an increased risk. Ascertaining affected relatives by lineage may prove to be more meaningful for risk estimation.

Our findings are consistent with the few studies that have reported no association between a first-degree family history of breast cancer and tumor subtype defined by ER/PR [16,33] or HER2 status [34]. In contrast, our results are discordant with the previously described association between a first-degree family history of breast cancer and increased basal-type tumor risk, possibly due to differences in the age composition of our study population [15]. However, our results suggest a first-degree family history may be associated with an increased risk of Luminal A tumors similar in magnitude to that described by Yang et al [15]. Since hormone negative and HER2 over-expressing tumors are more common among younger women [34-35], and among women with BRCA1 germline mutations [36], it is possible that the age composition of our study population can explain the lack of associations between family history and hormone negative and basal-type tumors. Including only disease-free women ≥40 years may have excluded those women in the overall population who are most likely to be diagnosed with hormone negative and basal-type tumors, thereby attenuating our risk estimates. Additionally, limited statistical power due to small sample size for the tumor subtype analyses may have affected our risk estimates.

The large number of enrollees in our study allowed us to conduct an in-depth analysis of the relation between family history and breast cancer risk among 75,169 women with 218,242 person-years at risk. Additionally, we were able to examine the association between tumor subtype and family history. Our prospective cohort study design helped eliminate the potential for recall bias that may have occurred in previous retrospective cohort or case control studies that have examined the family history and breast cancer risk association [6]. Relative to other comparable prospective cohort studies, the age range and personal characteristics of our study subjects were also less restricted allowing our risk estimates to be generalizable to a larger group of women [2,30,37]. Our study was not designed to generate a risk prediction model to compare the risk of breast cancer across different risk factors, however, our results suggest that including more detailed family history in risk prediction models, such as the Gail model, may be important.

There are, however, four notable limitations to our study that may have affected our results. First, our risk estimates may be lower than those previously described because we studied only disease-free women aged ≥40 years; previous studies have suggested that the influence of family history on breast cancer risk may be particularly high among women <40 years [1,7, 30,38]. Secondly, the age-specific breast cancer rates observed in our cohort were notably higher than those estimated for the U.S. population by SEER, but were similar to SEER's estimates for Washington State where the study took place [39]. This disparity may indicate that our results can be generalized only to regions of the U.S. that have demographic characteristics and screening practices similar to those in Washington State. Thirdly, the

proportion of women in our cohort who reported a family history of breast cancer was much higher than previously noted in the literature [40]. However, this may be due to our exclusion of women with an unknown or missing family history if they in fact had no family history of breast cancer, an increase in reporting of family history due to improved awareness of breast cancer in family members, or an increase in detection due to screening. Finally, the use of self-reported family history data may have resulted in misclassification and biased our risk estimates toward the null.

In conclusion, our results suggest that previous estimates of the association between family history and breast cancer risk have been inflated, and that, in the absence of a first-degree history, having a second-degree family history alone is not associated with an increased risk of breast cancer among women who have not been diagnosed with breast cancer before age 40. Our study also suggests that detailed collection of family history data could be simplified among women ≥40 years since the age at diagnosis of family members does not appear to modify the risk of breast cancer. The lineage of affected relatives may play a role in the determination of a woman's risk of breast cancer and needs further exploration in other cohorts.

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## Appendix A. Description of family history classification for study subjects

| Family History Exposure | Family History of Women Included[1] |
|---|---|
| ***No family history*** | No relatives with a positive history of breast cancer **(Referent group for all analyses)** |
| ***1st degree family history*** | |
| 1st degree history only | ≥ 1 affected first-degree relatives, no affected second- degree relatives |
| 1st and 2nd degree history | ≥ 1 affected first AND second-degree relatives |
| *Number of affected 1st degree relatives* | |
| 1 | 1 affected first-degree relative, regardless of second-degree history |
| ≥ 2 | ≥ 2 affected first-degree relatives, regardless of second-degree history |
| *Age of affected 1st degree relatives* | |
| ≥ 50 years only | ≥ 1 affected first-degree relative diagnosed ≥ 50 years, none diagnosed < 50 years, regardless of second-degree history |
| At least one <50 years | ≥ 1 affected first-degree relative diagnosed < 50 years, regardless of second-degree history |
| ***2nd degree family history*** | |
| 2nd degree history only | ≥ 1 affected second-degree relative, no affected first-degree relatives |
| *Number of affected 2nd degree relatives* | |
| 1 | 1 affected second-degree relative, no affected first-degree relatives |
| ≥ 2 | ≥ 2 affected second-degree relatives, no affected first-degree relatives |
| *Age of affected 2nd degree relatives* | |

| Family History Exposure | Family History of Women Included[1] |
|---|---|
| ≥ 50 years only | ≥ 1 affected second-degree relative diagnosed ≥ 50 years, none diagnosed < 50 years, and no first-degree history |
| At least one <50 years | ≥ 1 affected second-degree relative diagnosed < 50 years and no first-degree history |
| ***Specific Relative History***[2] | |
| *Number of affected relatives* | |
| 1 | 1 affected specific relative |
| ≥ 2 | ≥ 2 affected specific relatives |
| *Number of affected relatives and age at diagnosis* | |
| Only affected ≥ 50 years | |
| 1 | 1 relative diagnosed ≥ 50 years, none diagnosed < 50 years |
| ≥ 2 | ≥ 2 relatives diagnosed ≥ 50 years, none diagnosed < 50 years |
| ≥ 1 relative < 50 years | At least 1 relative diagnosed < 50 years |

[1] In only female relatives: mother, sister(s), aunt(s), daughter(s)

[2] For grandmother, sister, and aunt history

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**Table 1**

Demographic and reproductive characteristics of study subjects (N=75,169) as self-reported on the date of study entry

| *Characteristic* | All Study Subjects | | | Women with a Breast Cancer Diagnosis | | Breast Cancer Incidence Rate per 100,000[1] |
|---|---|---|---|---|---|---|
| | N | % | Person-Years at Risk | N | % | |
| *Mailed Surveys*[2] | 8,793 | 11.7 | 17,324 | 35 | 3.2 | 202 |
| *In Clinic Surveys*[3] | 66,376 | 88.3 | 201,100 | 1,052 | 96.8 | 523 |
| ***Age (years)*** | | | | | | |
| 40-44 | 11,887 | 15.8 | 30,064 | 71 | 6.5 | 236 |
| 45-49 | 12,184 | 16.2 | 33,562 | 133 | 12.2 | 396 |
| 50-54 | 15,121 | 20.1 | 43,831 | 158 | 14.5 | 360 |
| 55-59 | 11,284 | 15.0 | 33,139 | 169 | 15.6 | 510 |
| 60-64 | 7,302 | 9.7 | 21,763 | 140 | 12.9 | 643 |
| 65-69 | 5,293 | 7.0 | 16,654 | 125 | 11.5 | 751 |
| 70-74 | 4,557 | 6.1 | 14,735 | 108 | 9.9 | 733 |
| 75-80 | 3,808 | 5.1 | 12,357 | 92 | 8.5 | 745 |
| 80+ | 3,733 | 5.0 | 12,318 | 91 | 8.4 | 739 |
| ***Race*** | | | | | | |
| White | 62,475 | 83.5 | 184,465 | 949 | 87.7 | 514 |
| Black | 2,644 | 3.5 | 7,177 | 27 | 2.5 | 376 |
| American Indian | 3,124 | 4.2 | 8,983 | 43 | 4.0 | 479 |
| Asian | 5,857 | 7.8 | 15,514 | 55 | 5.1 | 355 |
| Other/Mixed | 742 | 1.0 | 1,655 | 8 | 0.7 | 483 |
| Missing | 327 | -- | 630 | 5 | -- | 794 |
| ***Body Mass Index (kg/m$^2$)*** | | | | | | |
| <25 | 30,911 | 42.9 | 90,324 | 434 | 41.8 | 480 |
| 25-30 | 21,161 | 29.4 | 61,733 | 328 | 31.6 | 531 |
| 30+ | 19.915 | 27.7 | 56,722 | 277 | 26.7 | 488 |
| Missing | 3,182 | -- | 9,646 | 48 | -- | 498 |
| ***Menopausal Status*** | | | | | | |
| Pre/Peri-Menopausal | 22,360 | 31.7 | 60,488 | 208 | 19.8 | 344 |
| Post-Menopausal | 48,219 | 68.3 | 145,428 | 844 | 80.2 | 580 |

| *Characteristic* | All Study Subjects | | | Women with a Breast Cancer Diagnosis | | Breast Cancer Incidence Rate per 100,000[1] |
|---|---|---|---|---|---|---|
| | N | % | Person-Years at Risk | N | % | |
| Missing | 4,590 | -- | 12,508 | 35 | -- | 280 |
| ***Age at Menarche (years)*** | | | | | | |
| ≤ 12 | 30,516 | 46.1 | 88,795 | 452 | 47.5 | 509 |
| 13 | 18,950 | 28.6 | 54,740 | 251 | 26.4 | 459 |
| 14 | 8,790 | 13.3 | 25,657 | 140 | 14.7 | 546 |
| 15+ | 7,987 | 12.1 | 22,620 | 109 | 11.5 | 482 |
| Missing | 8,926 | -- | 26,612 | 135 | -- | 507 |
| ***Age at 1st Birth (years)*** | | | | | | |
| Nulliparous | 13,206 | 17.9 | 38,379 | 166 | 15.7 | 433 |
| <20 | 11,285 | 15.3 | 32,325 | 141 | 13.3 | 436 |
| 20-24 | 23,337 | 31.6 | 68,376 | 380 | 35.8 | 556 |
| 25-29 | 14,998 | 20.3 | 43,254 | 216 | 20.4 | 499 |
| 30-34 | 7,568 | 10.3 | 22,181 | 115 | 10.8 | 518 |
| 35+ | 3,397 | 4.6 | 9,705 | 43 | 4.0 | 443 |
| Missing | 1,378 | -- | 4,205 | 26 | -- | 618 |
| ***Hormone Use*** | | | | | | |
| Never | 35,673 | 48.7 | 97,965 | 429 | 40.5 | 438 |
| Former | 17,565 | 23.9 | 48,993 | 248 | 23.4 | 506 |
| Current[4] | 20,086 | 27.4 | 66,428 | 382 | 36.1 | 575 |
| Progestin Only | 724 | 4.0 | 2,160 | 6 | 1.7 | 278 |
| Estrogen Only | 8,090 | 43.7 | 26,207 | 118 | 32.9 | 450 |
| Estrogen + Progestin | 9,704 | 52.4 | 33,081 | 235 | 65.4 | 710 |
| Missing | 1,796 | -- | 5,039 | 28 | -- | 556 |
| ***Breast density*** | | | | | | |
| Almost entirely fat | 2,788 | 4.1 | 7,917 | 18 | 1.9 | 227 |
| Scattered fibroglandular tissue | 20,738 | 30.8 | 62,447 | 203 | 20.8 | 325 |
| Heterogeneously dense | 34,943 | 51.9 | 105,123 | 609 | 62.5 | 579 |
| Extremely dense | 8,919 | 13.2 | 26,880 | 145 | 14.9 | 539 |
| Missing | 7,781 | -- | 16,058 | 112 | -- | 697 |

| *Characteristic* | All Study Subjects | | | Women with a Breast Cancer Diagnosis | | Breast Cancer Incidence Rate per 100,000[1] |
|---|---|---|---|---|---|---|
| | N | % | Person-Years at Risk | N | % | |
| ***Benign Breast Biopsy History*** | | | | | | |
| No | 61,141 | 82.7 | 175,709 | 791 | 74.4 | 450 |
| Yes | 12,831 | 17.3 | 39,218 | 272 | 25.6 | 694 |
| Missing | 1,197 | -- | 3,497 | 24 | -- | 686 |
| ***Mammogram within 3 years prior to baseline*** | | | | | | |
| No | 25,658 | 34.1 | 65,237 | 336 | 30.9 | 515 |
| Yes | 49,511 | 65.9 | 153,188 | 751 | 69.1 | 490 |

[1] Number of breast cancer diagnoses per 100,000 person-years

[2] Baseline questionnaire completed via mail by subject at age 40 or upon enrollment in Group Health

[3] Baseline questionnaire was filled out in clinic during a screening or diagnostic mammogram

[4] Number of specific hormone users may not add to total current hormone users due to missing data

**Table 2**

Multivariable hazard ratios (HR) and 95% confidence intervals (CI) of breast cancer associated with the degree of a woman's affected relatives[1]

| Relative with breast cancer | Subjects | Person-Years | Cases | Adjusted[2] HR (95%CI) |
|---|---|---|---|---|
| No family history (Ref.) | 44,421 | 127,114 | 558 | 1.0 |
| ***1st degree family history*** | 14,675 | 44,553 | 314 | 1.54 (1.34-1.77) |
| 1st degree history only | 8,355 | 25,329 | 181 | 1.52 (1.28-1.80) |
| 1st and 2nd degree history | 6,320 | 19,224 | 133 | 1.58 (1.30-1.90) |
| *Number of affected 1st degree relatives* | | | | |
| 1 | 12,392 | 37,328 | 252 | 1.51 (1.30-1.75) |
| 2+ | 1,947 | 6,215 | 56 | 1.76 (1.33-2.32) |
| *Age of affected 1st degree relatives* | | | | |
| ≥50 years only | 8,501 | 25,791 | 184 | 1.56 (1.32-1.84) |
| At least one <50 years | 5,177 | 15,723 | 99 | 1.42 (1.15-1.76) |
| ***2nd degree family history***[3] | | | | |
| 2nd degree history only | 16,073 | 46,758 | 215 | 1.15 (0.98-1.35) |
| *Number of affected 2nd degree relatives* | | | | |
| 1 | 10,793 | 31,387 | 158 | 1.25 (1.05-1.50) |
| 2+ | 5,280 | 15,370 | 57 | 0.94 (0.71-1.23) |
| *Age of affected 2nd degree relatives* | | | | |
| ≥50 years only | 7,283 | 21,262 | 104 | 1.23 (0.99-1.51) |
| At least one <50 years | 6,184 | 17,764 | 75 | 1.06 (0.84-1.36) |

[1] Estimated using Cox Proportional Hazards Models among women in the Group Health Breast Cancer Screening Program between June 1, 2001 and December 31, 2005

[2] Adjusted for age at baseline (quadratic) and stratified by source of risk factor information

[3] Among women with no affected 1st degree relatives

**Table 3**

Multivariable hazard ratios (HR) and 95% confidence intervals (CI) of breast cancer associated with a woman's specific type of affected relatives[1]

| Relative with breast cancer | Subjects | Person- Years | Cases | Adjusted[2] HR (95%CI) |
|---|---|---|---|---|
| ***Affected Maternal History*** | | | | |
| No Family History (Ref.) | 44,421 | 127,114 | 558 | 1.0 |
| Affected mother | 8,307 | 25,059 | 161 | 1.56 (1.31-1.86) |
| *Affected mother's age at diagnosis (years)* | | | | |
| ≥50 | 5,986 | 18,128 | 112 | 1.49 (1.22-1.83) |
| <50 | 1,986 | 5,926 | 35 | 1.50 (1.07-2.12) |
| ***Affected Grandmother History*** | | | | |
| No Family History (Ref.) | 44,421 | 127,114 | 558 | 1.0 |
| *No. of affected grandmothers* | | | | |
| 1 | 5,851 | 16,975 | 84 | 1.30 (1.03-1.64) |
| 2 | 324 | 930 | 9 | 2.66 (1.37-5.14) |
| *No. of affected grandmothers and age at diagnosis (years)* | | | | |
| Only affected ≥50 | | | | |
| 1 | 4,211 | 12,240 | 58 | 1.25 (0.95-1.64) |
| 2 | 171 | 492 | 6 | 3.46 (1.55-7.75) |
| At least one affected <50 | 1,733 | 4,989 | 28 | 1.48 (1.01-2.17) |
| ***Affected Sister History***[3] | | | | |
| No Family History (Ref.) | 32,445 | 92,122 | 390 | 1.0 |
| *No. of affected sisters* | | | | |
| 1 | 5,638 | 17,238 | 137 | 1.64 (1.34-2.00) |
| 2+ | 578 | 1,917 | 20 | 2.03 (1.29-3.19) |
| *No. of affected sisters and age at diagnosis (years)* | | | | |
| Only affected ≥50 | | | | |
| 1 | 2,753 | 8,504 | 78 | 1.77 (1.38-2.28) |
| 2+ | 224 | 740 | 10 | 2.49 (1.32-4.70) |
| At least one affected <50 | 2,947 | 8,994 | 59 | 1.50 (1.14-1.97) |
| ***Affected Aunt History***[4] | | | | |
| No Family History (Ref.) | 37,961 | 108,138 | 461 | 1.0 |
| *No. of affected aunts* | | | | |
| 1 | 11,792 | 34,958 | 188 | 1.30 (1.10-1.54) |
| 2+ | 3,768 | 11,167 | 59 | 1.28 (0.98-1.69) |
| *No. of affected aunts and age at diagnosis (years)* | | | | |
| Only affected ≥50 | | | | |
| 1 | 5,834 | 17,376 | 100 | 1.38 (1.11-1.72) |
| 2+ | 1,251 | 3,740 | 27 | 1.68 (1.14-2.48) |
| At least one affected <50 | 5,042 | 14,668 | 65 | 1.10 (0.85-1.43) |

[1] Estimated using Cox Proportional Hazards Models among women in the Group Health Breast Cancer Screening Program between June 1, 2001 and December 31, 2005

[2] Adjusted for age at baseline (quadratic) and stratified by source of risk factor information

[3] Among women with ≥1 sister who had complete sister history data

[4] Among women with ≥1 aunt who had complete aunt history data

**Table 4**

Age-adjusted hazard ratios (HR) and 95% confidence intervals (CI) of breast cancer tumor subtype associated with the degree of affected relatives[1]

| | ER+/PR+ | | ER+/PR- | | ER-/PR- | |
|---|---|---|---|---|---|---|
| **Relative with breast cancer** | **N** | **HR[1] (95%CI)** | **N** | **HR[1] (95%CI)** | **N** | **HR[2] (95%CI)** |
| No family history (Ref.) | 336 | 1.0 | 33 | 1.0 | 75 | 1.0 |
| 2nd degree history only | 124 | 1.11 (0.91-1.37) | 17 | 1.60 (0.89-2.87) | 27 | 1.02 (0.66-1.59) |
| Any 1st degree history | 181 | 1.49 (1.24-1.78) | 29 | 2.43 (1.47-4.01) | 36 | 1.36 (0.91-2.03) |

[1] Estimated using Cox Proportional Hazards models among women in the Group Health Breast Cancer Screening Program between June 1, 2001 and December 31, 2005

[2] Adjusted for age at baseline (quadratic)

**Table 5**

Age adjusted hazard ratios (HR) and 95% confidence intervals (CI) of breast cancer tumor subtype associated with the degree of affected relatives[1]

| | Luminal A[2] | | Luminal B[3] | | HER2-neu Over-expressing[4] | | Basal[5] | |
|---|---|---|---|---|---|---|---|---|
| **Relative with breast cancer** | **N** | **HR[6] (95%CI)** | **N** | **HR[6] (95%CI)** | **N** | **HR[6] (95%CI)** | **N** | **HR[6] (95%CI)** |
| No family history (Ref.) | 191 | 1.0 | 11 | 1.0 | 5 | 1.0 | 36 | 1.0 |
| 2nd degree history only | 75 | 1.23 (0.94-1.61) | 8 | 1.98 (0.79-4.94) | 9 | 4.87 (1.62-14.6) | 4 | 0.33 (0.12-0.93) |
| Any 1st degree history | 125 | 1.78 (1.42-2.23) | 8 | 2.10 (0.84-5.22) | 5 | 2.91 (0.84-10.1) | 13 | 1.01 (0.53-1.90) |

[1] Estimated using Cox Proportional Hazards models among women in the Group Health Breast Cancer Screening Program between June 1, 2001 and December 31, 2005

[2] ER+ and/or PR+, HER2-

[3] ER+ and/or PR+, HER2+

[4] ER-, PR-, HER2+

[5] ER-, PR-, HER2-

[6] Adjusted for age at baseline (quadratic)