

Family History, Ethnicity, and Relative Risk of Breast Cancer in a Prospective Cohort Study of Older Women¹

Thomas A. Sellers,² Amanda J. Walsh,
Dawn M. Grabrick, Kristin E. Anderson,
James R. Cerhan, and Aaron R. Folsom

Department of Health Sciences Research, Mayo Clinic and Mayo Clinic Cancer Center, Rochester, Minnesota 55905 [T. A. S., D. M. G., J. R. C.], and Division of Epidemiology, University of Minnesota School of Public Health, and University of Minnesota Cancer Center, Minneapolis, Minnesota 55454-1015 [A. J. W., D. M. G., K. E. A., A. R. F.]

Abstract

In a cohort of 27,578 postmenopausal Iowa women, we examined whether the risk with a family history of breast cancer differs by self-reported ethnicity. A total of 1042 breast cancer cases occurred over 10 years of follow-up. Using a phylogenetic tree, ethnicities were combined into five groups: Scandinavian; English, Scottish, Welsh, and Dutch (ESWD); Irish; German; and Other European. The incidence of breast cancer did not differ significantly by ethnicity, although the highest rates were observed among Scandinavian women (488 per 100,000 per year) and the lowest among Irish women (353 per 100,000 per year). The prevalence of a family history of breast cancer was not significantly associated with ethnicity when only first-degree relatives were considered ($P = 0.17$), but inclusion of data on second-degree relatives increased the statistical significance of the association ($P = 0.003$). Differences in mean levels of breast cancer risk factors between ethnicities were generally small but statistically significant. Proportional hazards regression was performed to evaluate potential interactions of family history with ethnicity on breast cancer incidence. A family history of breast cancer was associated with increased relative risks among ESWD, Germans, and Other Europeans but not among Irish and Scandinavians. Relative risk estimates were not attenuated upon addition of known breast cancer risk factors to the model, implying that the distribution of these risk factors by ethnicity is unlikely to explain some of the observed ethnic-specific differences between family history and risk of breast cancer. Results of this study could have implications for studies of common genetic polymorphisms and cancer risk.

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² To whom requests for reprints should be addressed, at Mayo Clinic, Department of Health Sciences Research, Rochester, MN 55905.

Introduction

International variation in the incidence rate of breast cancer is considerable. For example, the age-adjusted breast cancer incidence per 100,000 is >100 in California, between 25 and 40 in Latin America, and <10 in Africa (1). Migrant studies (2) have clearly demonstrated that a significant portion of the variability in incidence is attributable to differences in risk factor levels. Similarly, geographic variation within a country can also be partly influenced by population risk factor differences (3). Relatively little attention has been paid, however, to the extent that variation in risk is influenced by host differences in genetic variation or predisposition to the disease. Some of the international variation in breast cancer risk may in part be attributed to ethnic variation in the frequency of specific susceptibility genes.

One of the strongest risk factors for breast cancer is a family history of the disease (4). Although familial aggregation of breast cancer may occur for several reasons, including chance and shared environmental factors, several major genes have been identified that confer an increased susceptibility to breast cancer when inherited in a mutated form (5). Studies have suggested that the relative proportion of breast-ovarian cancer families due to mutations in *BRCA1* or *BRCA2* varies in different populations. For example, the percentage of breast-ovarian cancer families explained by *BRCA1* mutations is estimated to be 29% in Italy, 21% in Britain, and 9% in Iceland (6). In addition, in most populations *BRCA1* mutations are more common than *BRCA2* mutations in breast-ovarian cancer families, although in Iceland *BRCA2* mutations are more common than *BRCA1* mutations in this type of family (6).

Specific mutations identified in *BRCA1* or *BRCA2* also differ by ethnic group. In Israel, three specific mutations were reported to account for 36% of breast-ovarian cancer families (7). A specific *BRCA1* mutation, 185delAG, has been observed primarily in the Ashkenazi Jewish population (8, 9). The carrier frequency of the 185delAG mutation in an Ashkenazi Jewish population from the United States and Israel was determined to be 0.9%, which is higher than the 1 in 300 to 1 in 800 carrier estimate for the general population in the United States (10). The carrier frequency of a specific *BRCA2* mutation, 6174delT, is also increased in the Ashkenazi Jewish population (11). Johannsson *et al.* (12) found nine *BRCA1* mutations in 15 breast and ovarian cancer families in southern Sweden. Four mutations were identified repeatedly and showed evidence of founder effects. In addition, of the 15 families studied, 13 had mutations in exon 11. These were similar to the findings in a British study where 17 of 32 families had mutations in exon 11 (13). These Swedish and British families differed from the 10 German families with *BRCA1* mutations studied by Janddrig *et al.* (14) and Hamann *et al.* (15) in which no mutations in exon 11 were identified. In 79 Dutch and Belgian breast ovarian cancer families, 19 had the same 2804delAA mutation in *BRCA1*, a mutation that has not been reported outside of the

Table 1 Age-adjusted breast cancer incidence rates by primary ethnic affiliation in postmenopausal Iowa women

Ethnicity	No. of cases	Incidence rate per 100,000	95% confidence interval
English, Scotch, Welsh, Dutch	323	404	360–448
German	405	405	366–444
Irish	93	353	282–425
Norwegian, Swedish	127	488	403–572
Other European	94	400	320–481

Netherlands (16). In Iceland, 16 of 21 breast cancer families had the same *BRCA2* mutation, 999del5 (17). This mutation was identified in 0.6% of the general population in Iceland and has only been reported in two families outside of that country.

Specific mutations can confer different lifetime risks of cancer. For example, it appears that the *BRCA2* 6174delT mutation has a lower cumulative lifetime penetrance than the *BRCA1* 185delAG mutation (11), and the R841W mutation in *BRCA1* has been described as having a moderate phenotype, because it appears to be associated with later age at onset of breast cancer (18). Because specific mutations appear to confer different breast cancer risks, the variation in breast cancer risk in different populations might be attributed, in part, to underlying differences in genetic factors. These genetic differences may appear as ethnic-specific differences in breast cancer risk associated with a family history of the disease. This report presents an analysis of the association of family history with risk for breast cancer within specific ethnic groups in a large prospective cohort study of postmenopausal women.

Materials and Methods

The Iowa Women's Health Study is a prospective cohort study of postmenopausal women that has been described in detail elsewhere (19). Briefly, a questionnaire was mailed to a random sample of women between the ages of 55 and 69 years with a valid Iowa driver's license in 1986. Questionnaires were returned from 41,837 eligible women, representing a response rate of 42%. Nonrespondents have been characterized and found to have virtually identical occurrence of breast cancer (20). Among other items reported on the 1986 baseline questionnaire were sociodemographic variables (including education), detailed menstrual and reproductive histories, current height and weight (used for BMI³ calculation), waist and hip circumferences, and alcohol use (from a food frequency section of the instrument). Data on the history of breast cancer among mothers, grandmothers, aunts, sisters, and daughters of the respondents were also collected. No questions were asked regarding family size or age at onset of breast cancer nor was any attempt made to validate cancer history in family members.

A follow-up questionnaire sent in October 1987 collected data on ethnic background. Women were asked to identify the single best response to the question "Which of the following best describes your national origin or ancestry?" Thirteen choices were offered: Asian, Afro American, American Indian, Dutch, English/Scottish/Welsh, German, Irish, Norwegian, Swedish, Southern European, Eastern European, Central or Western European, or Other. There were too few women self-reporting their ethnicity as Asian, Afro-American, American

³ The abbreviations used are: BMI, body mass index; RR, relative risk; CI, confidence interval; WHR, waist-to-hip ratio.

Table 2 Distribution of reported family history of breast cancer by primary ethnic affiliation in postmenopausal Iowa women

Ethnicity	Family history category	First-degree relatives only		First- or second-degree relatives	
		n	%	n	%
English, Scotch, Welsh, Dutch	No	7566		6483	
	Yes	1077	12.5	2160	25.0
German	No	9369		8156	
	Yes	1377	12.8	2590	24.1
Irish	No	2492		2170	
	Yes	333	11.8	655	23.2
Norwegian, Swedish	No	2515		2170	
	Yes	329	11.6	674	23.7
Other European	No	2231		1984	
	Yes	289	11.5	536	21.3

Indian, or Other to permit stable estimates of risk, hence they were excluded from analysis. The remaining nine ethnic groups were collapsed into five categories, based on genetic similarity (21). The five groups were Dutch/English/Scottish/Welsh (DESW), German, Irish, Norwegian/Swedish (Scandinavian), and Southern European/Eastern European/Central European/Western European (Other European).

A cohort of women at risk for incident breast cancer was identified by excluding those who reported that they were premenopausal ($n = 569$), had a cancer other than skin cancer ($n = 2293$), or had a previous total or partial mastectomy ($n = 1870$). The initial cohort at risk therefore comprised 37,105 women. Exclusion of nonrespondents to the follow-up survey and those with missing information on ethnicity or family history reduced the sample size to 31,508 women. Further exclusion of the rare ethnic groups yielded an analysis cohort that numbered 27,578 women.

Follow-up for the occurrence of cancer in the cohort was performed with use of data from the State Health Registry of Iowa, which is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. New cases of breast cancer were identified through a computer program that matched cases listed in the Registry from 1986 through 1995 and study participants by name, zip code, birth date, and social security number. Length of follow-up for each woman was designated as the length of time from the completion of the baseline questionnaire to one of the following events, listed in descending order of priority: the date of diagnosis of breast cancer, the date of death (if death occurred in Iowa), the date the woman moved out of Iowa (if known), the midpoint of the interval between the last follow-up contact and December 31, 1995 (if the date of the woman's departure from Iowa was unknown), or the midpoint of the interval between the date of last contact and the date of death (for deaths in women who had moved from Iowa). Women for whom these criteria did not apply were assumed to be still living in Iowa and contributed follow-up data until December 31, 1995.

Person-years in each exposure category were accumulated for the entire cohort at risk and separately for those with a family history of breast cancer and those with no such family history. Incidence was calculated by dividing the corresponding number of new cases of breast cancer by the number of person-years of follow-up. Age-adjusted and multivariate-adjusted RRs were calculated using proportional-hazards models as implemented in the SAS program PHREG (22). The assumption

Table 3 Mean levels of measured breast cancer risk factors by primary ethnic identity in postmenopausal Iowa women

Risk factor	English, Scotch, Welsh, Dutch	German	Irish	Norwegian, Swedish	Other European
Age at menarche	12.8	12.9	12.8	13.0	12.8
Age at menopause ^a	47.8	48.1	47.1	47.8	48.0
Proportion ever pregnant	0.93	0.92	0.92	0.93	0.93
Number of pregnancies ^b	3.4	3.8	4.0	3.4	3.6
Age at first pregnancy	22.6	22.9	22.4	22.9	23.0
Proportion with high school education	0.46	0.36	0.40	0.47	0.41
BMI (kg/m ²)	26.9	27.0	27.0	26.5	27.0
WHR	0.834	0.836	0.848	0.828	0.837
Alcohol (grams/day) ^c	3.6	3.7	4.5	3.8	3.6

^a Includes both natural and surgical menopause.

^b Nulliparous women included in calculation of mean.

^c Nondrinkers included in calculation of mean intake of alcohol.

Table 4 Age and multivariate-adjusted relative risks of postmenopausal breast cancer associated with self-reported ethnicity and family history

Ethnicity	Family history	No. of cases	Age-adjusted RR	Multivariate-adjusted RR ^a	95% CI
Irish	No	80	1.00	1.00	
	Yes	13	1.21	1.26	0.70–2.28
English, Scottish, Welsh, Dutch	No	256	1.00	1.00	
	Yes	67	1.87	1.82	1.38–2.39
German	No	335	1.00	1.00	
	Yes	70	1.43	1.37	1.04–1.80
Norwegian, Swedish	No	111	1.00	1.00	
	Yes	16	1.08	1.04	0.60–1.79
Other European	No	79	1.00	1.00	
	Yes	15	1.48	1.52	0.87–2.66

^a Adjusted for age, age at menarche, age at menopause, ever pregnant, number of pregnancies, age at first pregnancy, educational level, BMI, WHR, and alcohol consumption.

of proportional hazards for the exposures of interest was tested and not found to be violated. The association of family history with breast cancer incidence was examined within strata defined by ethnicity. A test for interaction between family history and ethnicity was evaluated by entering cross-product terms in proportional-hazards models. For all RRs, 95% CIs were estimated. Differences in risk factor levels among women in different ethnic groups were assessed by means of analysis of covariance (adjusted for age).

Results

Because the data on ethnicity were collected at the first follow-up and participation was not complete, initial analyses were performed to compare participants and nonparticipants with respect to the distribution of risk factors and incidence of breast cancer. There were no major differences among the analytic cohort and those excluded for missing information on ethnicity or family history in the mean age at menarche (12.8 years *versus* 12.9 years), mean age at menopause (47.8 years *versus* 47.1 years), percent nulliparous (8% *versus* 9%), mean number of pregnancies (3.62 *versus* 3.55), mean age at first pregnancy (22.7 years *versus* 22.1 years), BMI (26.9 *versus* 27.3), waist-to-hip ratio (0.836 *versus* 0.846), or alcohol intake (3.7 *versus* 3.4 g per day), respectively. Study subjects with missing information on family history or ethnicity were less likely to have at least a high school education (28%) than subjects who provided this information (41%). A total of 201 cases of incident breast cancer occurred among the subset excluded from the analysis of ethnicity. The age-adjusted incidence rates for the analytic cohort (408 per 100,000 per year; 95% CI, 383–433) was not significantly different than the rate

among the subset excluded from analysis (415 per 100,000 per year; 95% CI, 358–472).

The breast cancer incidence rates were not statistically significantly different among ethnic groups, although Scandinavians appeared to have the highest rate and Irish the lowest (Table 1). Reported frequency of a family history of breast cancer in first-degree relatives was not significantly different among ethnicities ($P = 0.17$; Table 2). However, when data on history of breast cancer in second-degree relatives were taken into consideration, the association with ethnicity was statistically significant ($P = 0.003$).

The distribution of breast cancer risk factors by ethnic group is given in Table 3. The magnitude of difference among groups in the mean levels of the risk factors examined was generally small, yet all were statistically significant. In general, Irish women seemed to be most distinct from the other ethnic groups. They tended to have earlier menopause and age at first pregnancy, high gravidity, high WHR, and the greatest alcohol intake. The DESW group had a risk profile similar to that of the Scandinavian women: low parity, highest education levels, lowest BMI, and lowest WHR. German women tended to have similar risk profiles to Other Europeans: later average age at menopause.

Age-adjusted and multivariate-adjusted RRs for breast cancer by ethnicity and family history are shown in Table 4. Inspection of the age-adjusted RRs suggests that a family history of breast cancer is a risk factor among the ESWD (RR, 1.9), German (RR, 1.4), and Other European women (RR, 1.5) but less so for the Irish women (RR, 1.2) and Scandinavian women (RR, 1.1). These RRs were not attenuated after adjustment for other breast cancer risk factors. Family history was

associated with significantly elevated risk only among the ESWD, with a borderline statistically significant association among German women.

Discussion

This analysis was undertaken to determine whether the risk associated with a family history of breast cancer differs by ethnicity in a cohort of 27,578 postmenopausal women. Self-reported ethnicities were combined into five groups based on genetic similarity. Family history appeared to be associated with statistically significantly increased risk of breast cancer only among women of English, Scotch, Welsh, or Dutch extraction; the association among German women was slightly lower and of borderline statistical significance. Scandinavian women had the highest observed incidence rates of breast cancer, but the rates were not significantly different between negative and positive family history groups. The lack of association with family history did not appear to be a reflection of different risk factor profiles. Moreover, the reported frequency of a positive family history was not particularly unusual compared with the frequencies reported by other ethnic groups.

There is a sizeable literature on differences in cancer risk by ethnic group (summarized in Ref. 23). In general, ethnicity has been equated with minority status. Thus, the published studies on the topic are typically evaluations of incidence, mortality, and survival of blacks, Asian Americans (primarily Chinese, Japanese, and Filipino), Hispanics, American Indians, Native Hawaiians, and Alaska Natives. The majority population of whites has been considered a homogeneous collection. To our knowledge, this is the first report of variation in breast cancer frequency among various Caucasian ethnic groups.

The difference between age-adjusted RRs and multivariate-adjusted RRs was small in all ethnic groups. In an earlier nested case-control family study of breast cancer conducted among the IWHs cohort, we noted that the clustering of breast cancer in families was not accounted for by the distribution of risk factors among relatives (24). Because of the smaller sample size of that substudy, however, we are unable to further explore that observation with the family data stratified on ethnicity.

Our analysis revealed differences in family history-associated risk patterns for breast cancer among ethnic groups in postmenopausal women, raising the hypothesis that these risk patterns may be attributed to genetic variation. It is tempting to speculate how genetic variation could be associated with different risk patterns. For example, a common, moderately penetrant gene for breast cancer is a possible explanation for the higher rates of breast cancer observed for Scandinavians in both negative and positive family history groups when compared with the reference group. Low carrier rates for breast cancer susceptibility genes could potentially explain patterns of risk among Irish women for whom both negative and positive family history groups were observed to have low risks.

Limitations of this study must be considered. Groupings of ethnicity were determined by location on a principal-component map (21). Misclassifications of ethnicities may have resulted, although there is no evidence to support this. If this was the case, real differences among the ethnic groups may have been obscured. The accuracy of reported ethnicity is unknown; misclassification of individuals must have occurred because they were permitted to designate only one primary ethnicity. Reported family history of breast cancer was not validated. Previous studies have shown that the accuracy of reports of family history of breast cancer is high (25); therefore, this most likely did not substantially affect our findings. Information

regarding family size was not obtained; differences in family size could obscure real differences because women with larger families would be more likely to have an affected relative on the basis of chance. Finally, genomic DNA was not collected on this cohort, precluding a more direct test of the genetic variation hypothesis.

Although a family history of breast cancer is considered one of the most important risk factors for the disease, our study suggests that family history may vary in strength as a risk factor among ethnic groups. It is possible that this variability results, at least in part, from genetic differences among populations. Future studies will be important to determine whether these differences are real and whether they are due to genetic variation. This information may both increase our understanding of the etiology of breast cancer and better our ability to accurately estimate breast cancer risks. More importantly, the results may have implications for studies of genetic variation in metabolic activation/detoxification pathways. In particular, we find ourselves in an era of molecular epidemiology with increasing numbers of studies that examine the association of common genetic polymorphisms with disease risk. To the extent that ethnic groups differ with regard to allele frequencies and differ with respect to disease risk, then ethnicity could be an important confounder in such studies. This underscores the long recognized significance of careful selection of controls for case-control studies but takes it to a greater level of importance.

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