

CORRESPONDENCE

Re: Effect of BRCA1 and BRCA2 on the Association Between Breast Cancer Risk and Family History

A family history of breast cancer, which is common among patients with breast cancer, is associated with a threefold to fivefold increased risk of this disease. Germline mutations in BRCA1 and BRCA2 are very strong risk factors that lead to a positive family history, but it is unknown what portion of the family history and breast cancer association they account for. Claus et al. (1) addressed this question by use of data from the Cancer and Steroid Hormone Study (CASH). A statistical model was applied to identify women likely to be BRCA1 and BRCA2 mutation carriers based on family history. After excluding subjects likely to be mutation carriers, family history was still associated with a modest, statistically significant, increased risk of breast cancer.

We present calculations of the residual effect of family history among 3174 unrelated Ashkenazi Jewish women who are noncarriers of three BRCA founder mutations (185delAG and 5382insC in BRCA1 and 6174delT in BRCA2). Subjects were Washington (DC)-area women who volunteered for a study of familial cancer (2,3). The 89 women who tested positive for a founder mutation were excluded. The 260 women with a personal history of breast cancer were considered to be case patients and the 2914 unaffected women were considered to be control subjects. Age and other time-dependent covariates were censored at the time control subjects volunteered and at the age of breast cancer diagnoses for case patients. Odds ratios were calculated by use of multiple logistic regression and were adjusted for age, birth cohort, age at menarche, parity, age at first birth, menopausal status, and use of oral contraceptives.

Table 1 shows the influence of family history on the odds of breast cancer in all noncarriers and those censored before age 55 years, the latter group being

Table 1. Effect of family history on odds of breast cancer among Ashkenazi Jewish women who do not carry founder BRCA1 and BRCA2 mutations

Relatives with breast cancer	Odds ratio of breast cancer (95% CI)*		
	All noncarriers (n = 3174)	Noncarriers age <55 y (n = 2120)	CASH estimates†
None	1.0 (referent)	1.0 (referent)	1.0 (referent)
First-degree relatives only	1.5‡ (1.1–2.2)	1.4 (0.9–2.3)	2.1
Second-degree relatives only	1.0 (0.7–1.4)	1.2 (0.8–1.8)	1.2
First- and second-degree relatives	1.5§ (0.9–2.4)	1.4 (0.8–2.6)	1.2
No first-degree relatives	1.0 (referent)	1.0 (referent)	1.0 (referent)
Any first-degree relatives	1.5 (1.1–2.0)	1.4 (0.9–2.0)	NE¶
Mother only	1.3 (0.9–1.9)	1.2 (0.8–1.9)	2.0
Sister(s) only	1.6 (0.9–2.7)	0.8 (0.2–2.5)	1.7
Mother and sister(s)	2.9‡ (1.3–6.9)	5.3 (1.8–16.2)	2.2
No. of affected first-degree relatives (continuous)#	1.5 (1.2–1.9)	1.5‡ (1.1–2.2)	NE¶

*CI = confidence interval.

†From (1). CASH = Cancer and Steroid Hormone Study.

‡.01 < P < .05.

§.05 < P < .10.

||P < .01.

¶NE = not examined.

#This variable measured increase in breast cancer odds associated with the actual number of affected first-degree relatives a woman has. Each additional affected mother, sister, or daughter that a woman has increases her odds of breast cancer 1.5 times.

more comparable to the CASH data. In women without a founder mutation, odds of disease are significantly increased among those with affected first-degree relatives, but a history of breast cancer in second-degree relatives was not associated with increased risk. Women with both an affected mother and sister have the highest odds of breast cancer, but the best-fitting model of family history's influence shows the odds of disease significantly increase 1.5 times ($P = .002$) with each affected first-degree relative a woman has. As in the study by Claus et al., family history of ovarian cancer was not related to noncarriers' breast cancer risk (data not shown).

In general agreement with the study by Claus et al., we find that family history of breast cancer remains a significant risk factor among Jewish women who do not carry BRCA1 and BRCA2 founder mutations. Some of the residual effect may be due to BRCA1 and BRCA2 mutations other than those we tested for, although they are not likely to account for all of the effect (4). Since study subjects were not incident breast cancer cases and appropriately matched controls, our results may be biased if women with a positive family history discover their cancers earlier, increasing their survival and entrance into our cross-sectional study. In this cohort, however, survival does not statistically

differ between BRCA1 and BRCA2 carrier and noncarrier cases (5). It is also possible that genetic factors other than BRCA1 and BRCA2 account for the family history association. Additional studies, such as segregation analyses, might be used to determine whether the patterns observed here support the existence of other susceptibility genes for breast cancer.

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