

consented to prospective follow-up at the time of genetic testing were identified. The incidence of new breast and ovarian cancers in probands and their families since receipt of their genetic test results was determined by questionnaire. The expected number of cancers and standardized incidence ratios (SIRs) were determined from age-specific cancer incidence rates from the Surveillance, Epidemiology, and End Results (SEER) program by using the method of Byar. All statistical tests were two-sided. During 2534 women-years of follow-up in 165 kindreds, 19 new cases of breast cancer were diagnosed, whereas only 6.07 were expected (SIR = 3.13, 95% confidence interval [CI] = 1.88 to 4.89;  $P < .001$ ), and one case of ovarian cancer was diagnosed, whereas only 0.66 was expected (SIR = 1.52, 95% CI = 0.02 to 8.46;  $P = .48$ ). These results suggest that women from BRCA mutation–negative, site-specific breast cancer families are not at increased risk for ovarian cancer. [J Natl Cancer Inst 2005;97:1382–4]

## Risk of Ovarian Cancer in BRCA1 and BRCA2 Mutation–Negative Hereditary Breast Cancer Families

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Women from site-specific hereditary breast cancer families who carry a BRCA1 or BRCA2 mutation are at increased risk for ovarian cancer. It is less clear, however, whether individuals from hereditary breast cancer families who do not carry such a mutation are also at increased ovarian cancer risk. To determine whether women from BRCA mutation–negative hereditary breast cancer families are at increased risk for ovarian cancer, 199 probands from BRCA mutation–negative, site-specific breast cancer kindreds who

Women with deleterious mutations in the BRCA1 or BRCA2 genes have a 9- to 36-fold increased risk of breast cancer and a 6- to 61-fold increased risk of ovarian cancer compared with general population rates (1). Because of the incomplete sensitivity of current methods to detect mutations in BRCA1 and BRCA2 (2–4) and because of reports of breast and ovarian cancer kindreds that do not show linkage to either BRCA1 or BRCA2 (2,5), women from mutation–negative hereditary breast cancer families may be recommended to participate in ovarian cancer risk-reduction strategies, including intensive screening and/or risk-reducing surgery (6–8). However, such strategies may subject women whose ovarian cancer risks are not clear to inconvenience, expense, anxiety, invasive follow-up, and the sequelae of surgical menopause as a result of oophorectomy. To address this issue, we conducted a prospective study of women from BRCA mutation–negative, site-specific hereditary breast cancer kindreds to evaluate their risk of subsequent ovarian cancer.

Records of 1745 patients of the Clinical Genetics Service at Memorial Sloan-Kettering Cancer Center (MSKCC) who underwent testing for BRCA1 and

BRCA2 mutations from August 1, 1996, through July 31, 2002, and who provided written informed consent for prospective follow-up on one of two institutional review board–approved studies were reviewed. This cohort represented 95.8% of all individuals who underwent BRCA mutation testing at MSKCC during the study period. All BRCA mutation–negative, site-specific breast cancer kindreds with a living female proband were identified. We included probands if 1) the kindred had at least three cases of breast cancer in the same lineage, 2) one of the breast cancers in a kindred was diagnosed when the patient was younger than age 50 years, 3) no ovarian cancer was present anywhere in the lineage, and 4) BRCA mutation screening did not detect a deleterious or unclassified missense mutation in the proband's BRCA1 or BRCA2 gene. If the proband reported her heritage to be exclusively Ashkenazi, testing negative for the three Ashkenazi founder mutations was sufficient for study inclusion because testing for just these mutations has been shown to identify approximately 95% of detectable BRCA mutations in such individuals (9,10). We defined a proband as the youngest living individual with breast cancer in the kindred who had personally undergone BRCA mutation testing.

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See "Notes" following "References."

DOI: 10.1093/jnci/dji281

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**Table 1.** Participant demographics

Demographic	Value
Total No. of participants	165
Mean age, y (range)	51.6 (25–77)
Personal history of breast cancer, No. (%)	128 (77)
Mean age at diagnosis of breast cancer in probands, y (range)	48.5 (24–74)
Mean No. of breast cancers in kindred (range)	4.14 (3–9)
No. Ashkenazi Jewish (%)	110 (67)

We used this proband definition because BRCA mutation testing in these individuals, as opposed to kindred members who presented first but were unaffected or diagnosed with breast cancer at later age, would be most likely to provide informative results. If a family had no member who had both been diagnosed with breast cancer and had undergone genetic testing, the proband was defined as the first unaffected individual in the kindred who underwent testing. All probands were sent a detailed follow-up questionnaire to obtain clinical follow-up information and detailed information on new cancers that they and their first-degree and second-degree relatives might have developed. Probands who did not respond to the mailed questionnaire were contacted by telephone and asked to provide follow-up information via a structured interview.

For each kindred, the number of women-years at risk for the proband and her relatives was the difference between the date follow-up information was provided and the date genetic testing results were transmitted to the proband. Expected cancer incidence for probands and for all first-degree and second-degree relatives in the lineage at risk older than 18 years at the time that results were transmitted to the proband was based on age-specific Surveillance, Epidemiology, and End Results (SEER) rates from 1973 through 2001 in 5-year age groups, beginning with age 15 years and ending with age 85 years or older (11). If the age of a relative

in the same generation as the proband was not known precisely, we assumed it to be that of the proband. If the relative was in the earlier or subsequent generation, we assumed her age to be 25 years older or younger than the age of the proband, respectively. The observed women-years of risk were then multiplied by expected cancer incidence obtained from the SEER database to estimate the total expected number of cancers. Standardized incidence ratios (SIRs) were determined by calculating the ratio of observed to expected numbers of cancers. The 95% confidence intervals (CIs) were calculated by using the method of Byar (12). The chi-square test was used to calculate *P* values. All statistical tests were two-sided.

Two hundred and seven living female probands meeting the study criteria were identified and sent a study questionnaire. Eight questionnaires were returned because of incorrect contact information. Of the remaining 199 probands, 165 (83%) completed the study questionnaire either by mail or telephone interview. Demographics of the study participants are presented in Table 1. Study participants were less likely to be of Ashkenazi heritage than nonresponders (67% vs. 88%, *P* = .01). There were no other statistically significant differences in any demographic criteria between study participants and nonresponders.

During a mean follow-up of 40.6 months (range = 15.3–82.4 months),

seven of 165 probands and 12 of their 583 first-degree or second-degree female relatives had a new diagnosis of breast cancer, compared with 6.07 diagnoses that were expected among these 748 individuals (SIR = 3.13, 95% CI = 1.88 to 4.89; *P* < .001). The 19 cases of breast cancers were diagnosed in 17 different kindreds a mean of 2.2 years after the proband received genetic test results. The mean age at diagnosis was 54.9 years. No proband and only one first-degree relative had ovarian cancer diagnosed during the 2534 women-years of follow-up, compared with 0.66 that were expected in this cohort (SIR = 1.52, 95% CI = 0.02 to 8.46; *P* = .48). This case of ovarian cancer was diagnosed in a 64-year-old sister of a proband, 4 years after the proband received genetic test results. Table 2 shows observed versus expected numbers of breast and ovarian cancers when the cohort is stratified by degree of relation.

Previous studies in ungenotyped women with a personal and family history of breast cancer have suggested that these women are at increased risk of developing ovarian cancer compared with the general population (13,14). Because the percentage of women in these studies with a deleterious BRCA1 or BRCA2 mutation is unknown, the incremental risk for ovarian cancer in women from BRCA mutation–negative hereditary breast cancer families is unclear. Additionally, because current BRCA mutation detection techniques are only 63%–85% sensitive (2,15) and because linkage studies have suggested that 10%–12% of hereditary breast cancer families with one case of ovarian cancer do not segregate a BRCA1 or BRCA2 mutation (2), many cancer genetic services suggest that women in BRCA mutation–negative hereditary breast cancer families consider participation in ovarian cancer risk-reduction

**Table 2.** Standardized incidence ratios (SIRs) for breast and ovarian cancer with 95% confidence intervals (CIs)\*

Cancer	Cohort	No.	No. observed cancers	No. expected cancers	SIR (95% CI)	<i>P</i> value
Breast	Overall	748	19	6.07	3.13 (1.88 to 4.89)	<.001
	Probands	165	7	1.43	4.90 (1.96 to 10.11)	<.001
	First-degree relatives	321	8	2.46	3.25 (1.40 to 6.40)	.004
	Second-degree relatives	262	4	2.18	1.83 (0.49 to 4.69)	.17
Ovary	Overall	748	1	0.66	1.52 (0.02 to 8.46)	.48
	Probands	165	0	0.14	0.00 (NA to 25.60)	.45
	First-degree relatives	321	1	0.26	3.88 (0.05 to 21.60)	.22
	Second-degree relatives	262	0	0.26	0.00 (NA to 14.30)	.31

\*Confidence intervals were calculated by using the method of Byar (12). *P* values were calculated by the chi-square test. All statistical tests were two-sided. NA = not applicable (lower limits for 95% confidence interval cannot be calculated using the method of Byar when the SIR is zero).

strategies. Our results, if confirmed, may allow this approach to be modified.

There are several possible sources of bias in this study. First, it is possible that some Ashkenazi Jewish probands may have had an undetected nonfounder BRCA mutation. Second, in a subset of kindreds, the genotyped proband was unaffected. The inclusion of such unaffected probands could result in the ascertainment of kindreds with BRCA mutations that did not segregate in the proband. Finally, because only one individual was genotyped in the majority of kindreds, phenocopies (i.e., patients with sporadic cancer in the background of an inherited predisposition) may have also resulted in undetected BRCA mutations in a fraction of kindreds. In all three of these cases, the result would be a bias toward the null hypothesis with more ovarian cancers being observed than expected.

Although these results suggest that no increased risk of ovarian cancer is associated with site-specific hereditary breast cancer kindreds with a BRCA mutation-negative status, caution is advised before women from these families are counseled not to participate in ovarian cancer risk-reduction strategies because there are several important limitations of this study. Two-thirds of the women in the cohort were Ashkenazi Jewish, and it is possible that BRCA mutation testing in this group more effectively excludes the possibility of a deleterious mutation than in non-Ashkenazi populations. Additionally, our study was powered to detect a 3.5- to 4-fold increase in ovarian cancer risk compared with that of the general population. Detection of a smaller (2.5- to 3.0-fold) increase in ovarian cancer risk in a study with a comparable design would require 3800–7600 women-years of follow-up compared with the 2534 women-years of follow-up in this study. The level of risk detected in such a study would be comparable to that of an individual with a first-degree relative with ovarian cancer; currently such individuals are not recommended to participate

in ovarian cancer risk-reduction strategies outside of clinical trials (16).

Despite these limitations, the current study provides the first prospective evidence, to our knowledge, that women from BRCA mutation-negative, site-specific hereditary breast cancer families may not be at statistically significantly increased risk of subsequent ovarian cancer. If these results are confirmed by other studies, it may allow ovarian cancer risk-reduction strategies to be tailored to women from site-specific breast cancer kindreds.

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## NOTES

Supported in part by the Department of Defense Breast Cancer Research Program (DAMD17-03-1-0375 to N. D. Kauff, DAMD17-00-1-0355 to K. E. Hurley), the Koodish Fellowship Fund, the Lucius L. Littauer Foundation, the Frankel Foundation, and the Prevention, Control and Population Research Program of Memorial Sloan-Kettering Cancer Center.

Funding to pay the Open Access publication charges for this article was provided by the Prevention, Control and Population Research Program of Memorial Sloan-Kettering Cancer Center.

Manuscript received January 24, 2005; revised July 1, 2005; accepted July 6, 2005.