Original Article

Risk of Metachronous Breast Cancer After BRCA Mutation–Associated Ovarian Cancer

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BACKGROUND: This study sought to estimate the risk of breast cancer (BC) after a diagnosis of ovarian cancer (OC) associated with mutation of the *BRCA1/2* (breast cancer, early onset) genes (*BRCA*-OC). **METHODS:** The Memorial Sloan-Kettering Cancer Center and the University of Pennsylvania, clinical genetics databases were searched to identify women with *BRCA*-OC who participated in genetic testing and follow-up studies from 1995 to 2009. The primary objective was to determine the risk of developing BC after *BRCA*-OC. Overall survival (OS) and BC-free survival (BCFS) were determined by the Kaplan-Meier method; patients were censored at the time of last follow-up. **RESULTS:** A total of 164 patients had *BRCA*-OC (115 with *BRCA1*; 49 with *BRCA2*). Of these 164 patients, 152 developed OC prior to *BRCA* testing (median time to testing, 2.4 years [0.01-55 years]). Median follow-up from OC for those not developing BC was 5.8 years (0.25-55.6 years). There were 46 deaths, but none were due to BC. The 5- and 10-year OS were 85% (95% confidence interval [CI] = 0.78, 0.90) and 68% (95% CI = 0.59, 0.76), respectively. There were 18 metachronous BC diagnoses. The 5- and 10-year BCFS were 97% (95% CI = 0.92, 0.99) and 91% (95% CI = 0.82, 0.95), respectively. A subset of 64 women were tested either before or within 12 months of *BRCA*-OC. In this pseudo-incident subset, 5- and 10- year OS was 71% (95% CI = 0.53, 0.83) and 62% (95% CI = 0.44, 0.75), respectively, and 5- and 10-year BCFS were 100% and 87% (95% CI = 0.56, 0.96), respectively. **CONCLUSIONS:** OS was dominated by OC deaths. Metachronous BC risk was lower than reported for unaffected *BRCA* mutation carriers. These results support nonsurgical management of BC risk in women with *BRCA*-OC. ***Cancer*** **2013;119:1344-8.**

KEYWORDS: breast cancer, ovarian cancer, *BRCA1*, *BRCA2*, second primary, metachronous.

INTRODUCTION

Women with germline mutations in *BRCA1* (breast cancer, early onset 1) or *BRCA2* have an increased risk of developing breast and ovarian cancer, with a lifetime risk of 56% to 84% for breast cancer by age 70 years.[1-3] The estimated lifetime risk for ovarian cancer ranges from 36% to 63% for *BRCA1* mutation carriers and 10% to 27% for *BRCA2* mutation carriers.[3-6] Typically, breast cancer presents earlier than ovarian cancer, especially in *BRCA1* carriers[7]; the risk of developing a metachronous ovarian cancer is greatest for women with early-onset breast cancer (younger than 40 years at diagnosis) or with a family history of breast or ovarian cancer.[8] A large-scale historical cohort study looked at the risk of metachronous ovarian cancer after *BRCA* breast cancer and determined that the 10-year actuarial risk for *BRCA1* carriers was 12.7% and that for *BRCA2* carriers was 6.8%.[9] To our knowledge, no study has examined the likelihood of developing metachronous breast cancer after *BRCA* ovarian cancer. We present data from follow-up studies of women with deleterious mutations in *BRCA1* or *BRCA2* to delineate the risk of breast cancer after a primary diagnosis of *BRCA* ovarian cancer.

MATERIALS AND METHODS

Study Subjects

The clinical genetics databases of Memorial Sloan-Kettering Cancer Center, New York, NY, and the University of Pennsylvania, Philadelphia, Pa, were queried to identify women with *BRCA* mutation–associated ovarian cancer (BRCA-OC) who have participated in genetic testing and follow-up studies from 1995 to 2009. Women were initially considered to be eligible for this study if they were ascertained for genetic testing because of a diagnosis of ovarian cancer, or if they developed (BRCA-OC) during prospective follow-up after ascertainment as an unaffected individual. All women had mutations that are predicted to be deleterious. Women were excluded if they had a diagnosis of breast cancer at or before the

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TABLE 1. Characteristics of Breast Cancers Diagnosed in Subjects

Characteristic		No. of Subjects
Stage		
	0	1
	I	8
	II	3
	III	1
	Unknown	5
Receptors		
	ER and/or PR+	5
	ER– and PR–	9
	HER2+	0
	Unknown	4
Detection		
	Mammography[a]	9
	MRI[b]	3
	Clinical breast examination	1
	Other[c]	2
	Unknown	3

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; PR, progesterone receptor.
[a] 9 had not had MRI screening.
[b] 2 had negative mammography within 6 months; 1 evident on same-day mammography.
[c] Incidental computed tomography abnormality.

diagnosis of *BRCA* ovarian cancer. The primary objective of the study was to determine the incidence and time to diagnosis of breast cancer in women with *BRCA* ovarian cancer.

Study Protocol

The study protocol was reviewed and approved by the institutional review boards of each participating center. Medical treatment records and pathology reports were reviewed. Information abstracted from the medical charts included date of ovarian cancer diagnosis, dates of recurrence, date of *BRCA* mutation testing, date of receipt of risk-reducing mastectomy (RRM), date of second malignancy, date of last follow-up, current vital status (living/deceased) and cause of death. Women were censored at last follow-up, date of RRM (if unaffected by breast cancer before surgery), or death (from any cause) for determination of breast cancer-free survival (BCFS). Overall survival (OS) was determined using Kaplan-Meier analysis with patients being censored at the time of last follow-up. We also performed a subanalysis of OS and BCFS by *BRCA* mutation status.

Statistical Analysis

OS and BCFS were analyzed using the Kaplan-Meier method. Differences by *BRCA1*/*BRCA*2 mutation status were assessed using the log-rank test. Confidence intervals for 5- and 10-year estimates were calculated using the log-log transformation. Secondary analyses were calculated using the competing risk methodology proposed by Fine and Gray.[10] To address potential survival bias, we also performed left-truncated analyses.[11] We also analyzed a "pseudo-incident" subset of the subjects who were tested either before or within 1 year after their diagnosis of ovarian cancer. All analyses were performed using the SAS and R programs.

RESULTS

A total of 167 (83 from Memorial Sloan-Kettering Cancer Center, 84 from University of Pennsylvania) women with primary *BRCA* ovarian cancer were ascertained. Of these, 2 women with synchronous *BRCA* ovarian cancer and *BRCA* breast cancer diagnoses were excluded from analysis, as was a woman with a low-grade borderline ovarian cancer at age 18. The final cohort consisted of 164 patients (115 with *BRCA1* mutation and 49 with *BRCA2* mutation) who were treated for a primary diagnosis of either ovarian, primary peritoneal, or fallopian tube cancer between 1995 and 2009. Median age at ovarian cancer diagnosis was 50 years (range, 24-83). Most (156 of 164) patients were white, and 91 of 164 patients either reported Ashkenazi Jewish ethnicity or carried an Ashkenazi founder mutation (62 with *BRCA1* 185delAG or 5382insC; 29 with *BRCA2* 6174delT). Median follow-up from ovarian cancer for those women who did not develop breast cancer (N=147) was 70.6 months (range, 3-391). Six patients underwent bilateral preventive RRM at a median of 23 months after their ovarian cancer diagnosis (range, 7-157). Eighteen patients (14 *BRCA1* and 4 *BRCA2*) developed breast cancer after *BRCA* ovarian cancer. Characteristics of the breast cancers and means of diagnosis are described in Table 1. Median time to breast cancer after ovarian cancer was 108 months (range, 13-241). There were a total of 46 deaths; none was reported as being due to breast cancer. In the entire group, 5- and 10-year OS was 85% (95% confidence interval [CI] = 0.78-0.90) and 68% (95% CI = 0.59-0.76) (Table 2). The 5- and 10-year BCFS was 97% (95% CI = 0.92-0.99) and 91% (95% CI = 0.82-0.95). For women with a *BRCA1* mutation, 5- and 10-year OS was 85% (95% CI = 0.76-0.91) and 65% (95% CI = 0.53-0.75), respectively. The 5- and 10-year BCFS for women with *BRCA1* mutation was 96% (95% CI = 0.90-0.99) and 88% (95% CI = 0.76-0.94) respectively. The 5- and 10-year OS for women with *BRCA2* mutation was 85% (95% CI = 0.69-0.93) and 75% (95% CI = 0.57-0.86). The 5- and 10-year BCFS for women with a *BRCA2* mutation was 98% (95% CI = 0.86-1.00) (Fig. 1). Breast cancer–free survival was

TABLE 2. Outcomes

Cohort	5-y OS (%) (95% CI)	10-y OS (%) (95% CI)	5-y BCFS (%) (95% CI)	10-y BCFS (%) (95% CI)
Entire cohort (N = 164)	85 (0.78-0.90)	68 (0.59-0.76)	97 (0.92-0.99)	91 (0.82-0.95)
BRCA1 (N = 115)	85 (0.76-0.91)	65 (0.53-0.75)	96 (0.90-0.99)	88 (0.76-0.94)
BRCA2 (N = 49)	85 (0.69-0.93)	75 (0.57-0.86)	98 (0.86-1.00)	98 (0.86-1.00)
Pseudo-incident cohort (N = 64)	71 (0.55-0.83)	62 (0.44-0.75)	100	87 (0.56-0.96)
BRCA1 (N = 44)	71 (0.50-0.84)	63 (0.41-0.78)	100	81 (0.42-0.95)
BRCA2 (N = 20)	72 (0.41-0.89)	58 (0.23-0.81)	100	100

Abbreviations: BCFS, breast cancer–free survival; CI, confidence interval; OS, overall survival.

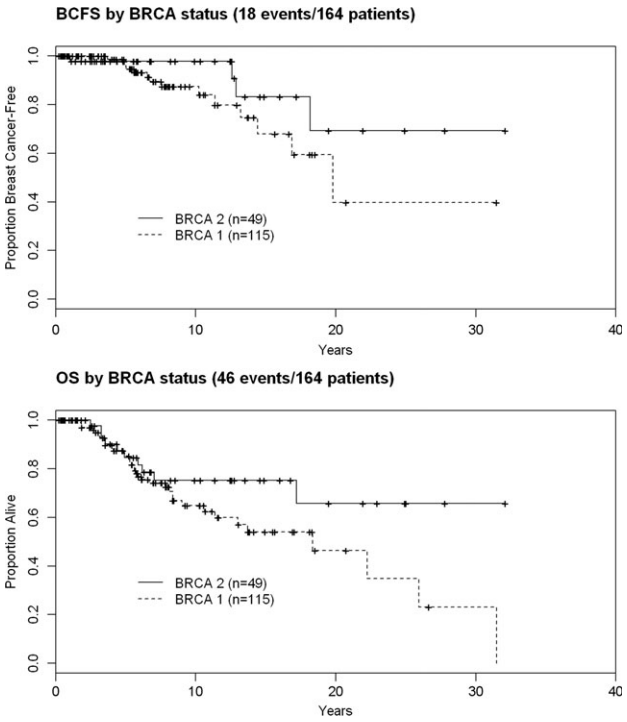

Figure 1. Breast cancer–free survival (BCFS; top panel) and overall survival (OS; bottom panel) is shown in all patients.

nearly identical when it was calculated by a competing risk methodology to account for the fact that many subjects died of ovarian cancer (data not shown).

Most subjects (n = 149) were tested after their diagnosis of ovarian cancer. Median time from ovarian cancer to *BRCA* testing was 26 months (range, 2 days to 375 months). Fifteen women were tested between 1 and 101 months before developing ovarian cancer. The survival experience of a prevalent ascertainment may not be reflective of newly diagnosed *BRCA* mutation carriers. To address this possibility, we identified a pseudo-incident cohort of 64 women (44 with BRCA1, 20 with *BRCA2*) who were tested either before or within 1 year after their diagnosis of *BRCA* ovarian cancer. In these women, OS after ovarian cancer was 71% (95% CI = 0.55-0.83) at 5 years and 62% (95% CI = 0.44-0.75) at 10 years. BCFS in this pseudo-incident subset was 100% at 5 years after ovarian cancer and 87% (95% CI = 0.56-0.96) at 10 years. The 5- and 10-year OS for the 44 *BRCA1* mutation carriers in this pseudo-incident subset was 71% (95% CI = 0.50-0.84) and 63% (95% CI = 0.41-0.78). BCFS in BRCA1 carriers was 100% at 5 years and 81% (0.42-0.95) at 10 years. The 5- and 10-year OS for the 20 *BRCA2* mutation carriers was 72% (95% CI = 0.41-0.89) and 58% (95% CI = 0.23-0.81), respectively. No breast cancers developed in *BRCA2* carriers in the "pseudo-incident" cohort; therefore, 5- and 10-year BCFS for patients with a *BRCA2* mutation was 100% (Table 1; Fig. 2). We also adjusted for the prevalent ascertainment by conducting a "left-truncated" analysis in the entire group of 149 women, wherein follow-up for breast cancer events was calculated from time of testing (or ovarian cancer diagnosis, for women tested before their diagnosis) to last follow-up. Breast cancer–free survival estimates by this method were nearly identical to those calculated by conventional Kaplan-Meier analysis beginning at time of ovarian cancer diagnosis (98% at 5 years from testing, 93% at 10 years).

DISCUSSION

To our knowledge, this is the first series to examine the risk of breast cancer after ovarian cancer in patients with *BRCA1* and *BRCA2* mutation. We demonstrate that the risk of metachronous breast cancer in the 5 years after a diagnosis of *BRCA* ovarian cancer is limited, and that survival is dominated by ovarian cancer–related mortality. At 10 years of follow-up, the probability that a survivor would develop breast cancer was less than 10%. However, because substantial proportion of women died from their ovarian cancer, the risk that a woman with newly diagnosed *BRCA* ovarian cancer will develop breast cancer during follow-up is even lower. These observations argue against aggressive surgical management of breast cancer risk in women with *BRCA* ovarian cancer, at least in the first 5 years after their ovarian cancer diagnosis.

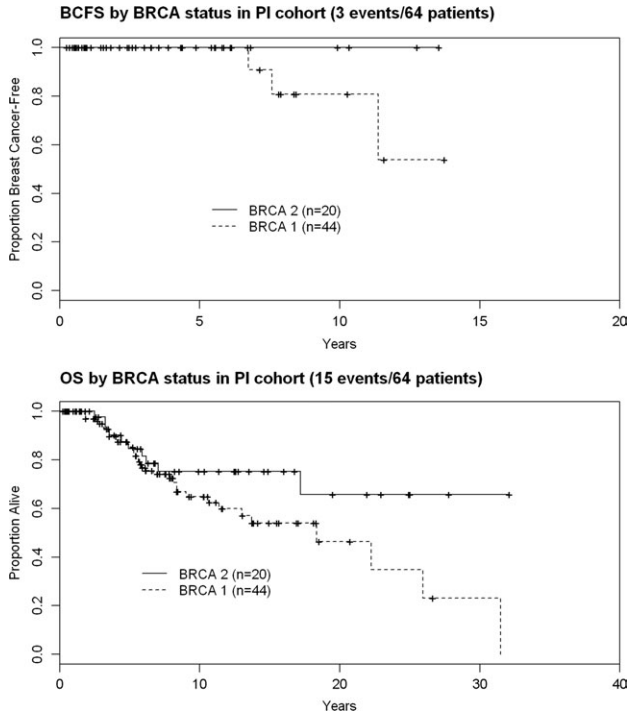

Figure 2. Breast cancer–free survival (BCFS; top panel) and overall survival (OS; bottom panel) is shown in the pseudo-incident (PI) cohort of women tested before or within 1 year after ovarian cancer diagnosis.

The current study has several strengths. To our knowledge, this is the first series of significant size that addresses the risk of metachronous breast cancer after *BRCA* ovarian cancer. It includes patients from 2 different academic institutions with similar experience. Because of the size of our study, we were able to address the potential for survival bias inherent in testing a prevalent cohort by evaluating the OS and BCFS in a pseudo-incident cohort (those tested before or within 1 year of ovarian cancer diagnosis). The breast cancer risk estimate from the overall study group did not appear to be higher than in the pseudo-incident subset, despite apparently better survival. However, the pseudo-incident group was relatively small, and follow-up was not long, leaving open the possibility that the breast cancer risk estimate in this subset of subjects may not be robust. As expected, the OS appeared to be somewhat worse in the pseudo-incident cohort, compared to the group as a whole. The survival experience of the pseudo-incident cohort was more similar to other series of *BRCA*-ovarian cancer reported to date,[12-14] suggesting that these women are likely to be more representative of patients with *BRCA* ovarian cancer. Several studies have also demonstrated that women with *BRCA* ovarian cancer have better survival compared to sporadic cancers.[12,14,15] The 5-year OS of 71% in the pseudo-incident group was still greater, however, than that observed in several other studies,[12,14-17] suggesting the possibility of a residual survival bias. To address this possibility, we also conducted a left-truncated analysis, wherein follow-up for breast cancer was calculated from the time of testing rather than breast cancer diagnosis. There were no meaningful differences in risk estimates when this methodology was used compared to the initial analysis.

Despite the somewhat improved survival in our study population, patient outcome was still dominated by ovarian cancer deaths. A large number of competing survival events other than those of interest can distort Kaplan-Meier estimates of the event of interest.[18] In this study, estimates of breast cancer–free survival were similar whether the analysis was conducted using conventional Kaplan-Meier analysis or a competing risk methodology. No deaths were reported from metachronous breast cancer, and most women with breast cancer had early-stage disease.

In this study, the risk that a survivor of *BRCA* ovarian cancer would develop breast cancer after a 10-year interval was 12% in BRCA1 carriers and 2% in BRCA2 carriers. These risks appear to be lower than the breast cancer risks described in unaffected carriers of similar age to the study group (16%-31% for BRCA1 mutation carriers and 9.5%-15% for BRCA2 carriers).[3,19] Possible explanations for a difference in BC risk in *BRCA* ovarian cancer survivors compared to unaffected mutation carriers are that treatment of ovarian cancer involves termination of ovarian function and use of platinum-based therapy, which could reduce the risk of subsequent breast cancer, or that women who have not developed breast cancer before ovarian cancer may have either genetic or nongenetic modifiers that are associated with lower breast cancer risk resulting from BRCA mutations. Women with recent diagnoses of ovarian cancer also may not be undergoing radiographic screening with the same intensity as unaffected women, which could lead to lower rates of diagnosis. Detailed information was not available regarding the screening practices of the subjects in this study. However, in a recent prospective study of breast cancer incidence in mutation carriers undergoing magnetic resonance imaging (MRI) surveillance, the breast cancer incidence was not substantially different from that observed in a historical comparison group of women undergoing mammogram screening alone, although stage at diagnosis was lower in the MRI-screened women.[20] This suggests that relatively few BRCA mutation–related breast cancers remain clinically occult, consistent with their generally poor differentiation and high mitotic rates, and that it is

unlikely that breast cancers were underdiagnosed in the women in this study.

In conclusion, the relatively low incidence of clinically diagnosed breast cancer in our series and the significant mortality risk from ovarian cancer suggest that nonsurgical management of breast cancer risk is most appropriate in women with a *BRCA* ovarian cancer diagnosis, particularly in the first 5 years after ovarian cancer diagnosis. This is especially the case for women with *BRCA2* mutations, who appeared to be at very low risk for metachronous breast cancer. Because our sample size was relatively small, it will be necessary to confirm our results in larger cohorts, preferably with prospective follow-up. These data should provide reassurance regarding breast cancer risk, however, to women with recently diagnosed *BRCA* mutation–associated ovarian cancer. Our findings suggest that the inherited breast cancer risk may still warrant careful surveillance in women who survive for a significant time (eg, more than 5 years) after their ovarian cancer diagnosis, particularly in light of several studies indicating a relatively favorable prognosis for some women with this disease.

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CONFLICT OF INTEREST DISCLOSURE

The authors made no disclosure.

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