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Association between basal-like phenotype and *BRCA1/2* germline mutations in Korean breast cancer patients

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ABSTRACT

Introduction *BRCA* mutation testing allows index patients and their families to be provided with appropriate cancer risk-reduction strategies. Because of the low prevalence of *BRCA* mutations in unselected breast cancer patients and the high cost of genetic testing, it is important to identify the subset of women who are likely to carry *BRCA* mutations. In the present study, we examined the association between *BRCA1/2* germline mutations and the immunohistochemical features of breast cancer.

Methods In a retrospective review of 498 breast cancer patients who had undergone *BRCA* testing at Seoul National University Bundang Hospital between July 2003 and September 2012, we gathered immunohistochemical information on estrogen receptor (ER), progesterone receptor (PR), HER2 (human epidermal growth factor receptor 2), cytokeratin 5/6, EGFR (epidermal growth factor receptor), and p53 status.

Results Among the 411 patients eligible for the study, 50 (12.2%) had germline mutations in *BRCA1* or *BRCA2*. Of the 93 patients with triple-negative breast cancer (TNBC), 25 with *BRCA1/2* mutations were identified (*BRCA1,* 20.4%; *BRCA2,* 6.5%). On univariate analysis, ER, PR, cytokeratin 5/6, EGFR, and TNBC were found to be related to *BRCA1* mutations, but on multivariate analysis, only TNBC was significantly associated with *BRCA1* mutations. Among patients with early-onset breast cancer or with a family history of breast or ovarian cancer, *BRCA1* mutations were significantly more prevalent in the TNBC group than in the non-TNBC group.

Conclusions In the present study, TNBC was the only independent predictor of *BRCA1* mutation in patients at high risk of hereditary breast and ovarian cancers. Other histologic features of basal-like breast cancer did not improve the estimate of *BRCA1* mutation risk.

Key Words Basal-like phenotype, *BRCA1*, *BRCA2*, triple-negative breast cancer

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INTRODUCTION

Individuals with a *BRCA1/2* genetic mutation are at high risk of developing breast, ovarian, prostate, pancreatic, and other cancers during their lifetime. The risks are 40%–80% for breast cancer, 11%–40% for ovarian cancer, 1%–10% for male breast cancer, and up to 39% for prostate cancer[1,2]. Identifying *BRCA* gene mutations is important so that cancer risk-reduction strategies can be provided both to the index patients and to their family members. However, because of the low prevalence of *BRCA* mutations in unselected breast cancer patients and the high cost of genetic testing, selecting appropriate subjects for testing is important. Many centres recommend genetic testing for women whose probability of harboring a *BRCA* gene mutation exceeds 10%[3].

Recently, many studies have reported that, compared with other breast cancer subtypes, triple-negative breast cancer (TNBC)—that is, tumours negative for estrogen receptor (ER), progesterone receptor (PR), and HER2 (human epidermal growth factor receptor 2) on immunohistochemical (IHC) testing—is associated with a higher prevalence of *BRCA1* mutations, especially in younger individuals[4–6]. The National Comprehensive Cancer

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Network guidelines include TNBC patients 60 years of age or less in the eligibility criteria for genetic testing[7]. However, the literature shows a wide range of variation in the prevalence of *BRCA1* mutations in TNBC patients[4,5,8]. Several studies have reported that TNBC alone, without other risk factors, is not an appropriate independent criterion for genetic testing and have recommended that additional risk factors be evaluated[9–11].

The IHC features of *BRCA1*-related breast cancer are similar to those of basal-like breast cancer, both usually displaying negativity for ER, PR, and HER2. Both are also characterized by overexpression of EGFR (epidermal growth factor receptor) and basal cytokeratins, and by negativity for phosphate and tensin homologue (PTEN), which are considered to be predictors for *BRCA1* mutation[8,12–15].

We therefore studied the association between *BRCA1/2* germline mutations and the IHC features of breast cancer to determine whether those features are independent predictors of *BRCA1* mutations in Korean breast cancer patients.

METHODS

Our retrospective review considered 498 patients who were diagnosed with breast cancer and underwent *BRCA1/2* genetic testing at Seoul National University Bundang Hospital between July 2003 and September 2012. Of those patients, 82 with ductal carcinoma *in situ* or microinvasive carcinoma were excluded from the analysis. Among the patients who had undergone *BRCA* genetic testing, 5 were also excluded because they were not the index patient in their family. Thus, the final analysis was based on 411 index patients with invasive breast cancer. Personal and family histories of breast or ovarian cancer and age at the time of diagnoses of breast cancer were obtained from medical records, and IHC findings about hormone receptor, HER2, cytokeratin 5/6 (CK5/6), EGFR, and p53 status were obtained from pathology reports. The study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB no. B-1212/184-301).

BRCA1/2 Analysis

All patients met at least one of the following testing criteria for *BRCA* mutational screening: breast cancer patient with a family history of breast or ovarian cancer, patient with early-onset breast cancer (age at diagnosis $\leq$ 40 years), bilateral breast cancer, multi-organ cancer, or male breast cancer. The median interval between breast cancer diagnosis and genetic testing was 15 days. *BRCA1* and *BRCA2* mutation analyses were performed by direct DNA sequencing and multiplex ligation-dependent probe amplification.

IHC Analysis

Expression of standard biomarkers including ER, PR, HER2, and p53 was evaluated in formalin-fixed paraffin-embedded whole-tissue sections at the time of diagnosis. Cytokeratin 5/6 and EGFR were evaluated later in the course of the present study. Formalin-fixed paraffin-embedded tissue sections (4 μm) were dried, deparaffinized, and rehydrated using standard procedures. Staining for IHC was performed on a BenchMark XT autostainer (Ventana Medical Systems, Tucson, AZ, U.S.A.) and an i-View detection kit (Ventana Medical Systems) for ER (1:100, clone SP1: Lab Vision Corporation, Fremont, CA, U.S.A.), PR (1:70, PgR 636: Dako Corporation, Glostrup, Denmark), HER2 (1:700, polyclonal: Dako Corporation), p53 (1:600, D07: Dako Corporation), and CK5/6 (1:50, clone D5/16 B4: Dako Corporation). Expression of EGFR was detected using EGFR pharmDx (Dako Corporation).

Triple-negative breast cancer was defined as IHC negativity for ER, PR, and HER2. A cut-off value of less than 1% was used to determine ER and PR negativity. Negative HER2 status was accepted when IHC was scored as 0 or 1+ or when HER2 was not detected by fluorescence *in situ* hybridization or silver *in situ* hybridization. Although samples from 3 patients whose HER2 IHC score was 2+ were not tested by either fluorescence or silver *in situ* hybridization, all were ER-positive, and the patients were therefore classified as non-TNBC. Positivity for EGFR was accepted when IHC was scored 2+ or 3+. Positivity for CK5/6 was accepted if any invasive tumour cells showed cytoplasmic staining. Of the 93 TNBC patients, 68 with adequate formalin-fixed paraffin-embedded tissue blocks were examined for PTEN negativity using an anti-PTEN antibody (Y184: GeneTex, Irvine, CA, U.S.A.). Negativity for PTEN was accepted if PTEN staining was undetectable in tumour cells when compared with adjacent normal stromal cells.

Statistical Analysis

Prevalence of *BRCA1/2* mutations was analyzed according to IHC features and was compared between the TNBC and non-TNBC groups on the basis of family history and age, using the Pearson chi-square test or Fisher exact test. Multivariate analysis by logistic regression was performed to estimate the value of selected variables to predict for *BRCA1* or *BRCA2* mutation. All statistical tests were performed using the IBM SPSS Statistics software application (version 21.0: IBM, Armonk, NY, U.S.A.). A p value less than 0.05 was considered to be statistically significant.

RESULTS

Characteristics of the Study Population

Table I presents the characteristics of the study population. Of the 411 eligible patients, 50 (12.2%) had germline mutations in *BRCA1* (6.1%) or *BRCA2* (6.1%). In patients with a family history of breast cancer, the rate of *BRCA1/2* mutation was 18.9%; in patients with a family history of ovarian cancer, the rate was 42.1%. The prevalence of *BRCA1/2* mutation was 12.9% in early-onset patients and 19.6% in patients with bilateral breast cancer. However, when patients with a family history were excluded, the rate of *BRCA1/2* mutation was 8.8% in early-onset patients and 10.0% in patients with bilateral breast cancer. There was no difference in mean age between patients with *BRCA1/2* mutation and those with no mutation (40.7 years vs. 42.7 years, $p = 0.281$); but patients with *BRCA1* mutation were younger than those with no mutation (34.8 years vs. 42.7 years, $p < 0.001$).

IHC Features of *BRCA1* and *BRCA2* Tumours

Table II shows the frequency of *BRCA* mutations according to expression of CK5/6, EGFR, p53, ER, PR, HER2, and TNBC.

On univariate analysis, statistically significant differences in *BRCA1* mutation rates were observed depending on the expression of CK5/6, EGFR, ER, PR, and TNBC. No difference in the prevalence of *BRCA2* mutations in the presence of a basal-like phenotype were observed (Table II). To identify independent predictors of *BRCA1* mutation, we performed a multivariate analysis based on CK5/6, EGFR, p53, and TNBC. On multivariate analysis, ER, PR, and HER2 were excluded because they interacted with TNBC, and only TNBC showed an association with *BRCA1* mutations (Table III).

Comparison of *BRCA* Mutation Rates in TNBC and Non-TNBC Patients

BRCA1/2 mutations were significantly more prevalent in TNBC patients than in non-TNBC patients (26.9% vs. 7.9%, $p < 0.001$). In patients with a family history of breast or ovarian cancer, the prevalence of *BRCA1/2* mutations was higher in those with TNBC than in those with non-TNBC regardless of age at diagnosis with breast cancer (40.0% vs. 11.9%, $p < 0.001$). In patients without a family history of breast or ovarian cancer, the overall prevalence of

TABLE I Characteristics of the study population by mutation status

Characteristic	Overall		*BRCA1*		*BRCA2*		*BRCA1/2*		Non-*BRCA*	
	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)
Overall cohort	411	100.0	25	6.1	25	6.1	50	12.2	361	87.8
Mean age (years)	42.5		34.8		46.6		40.7		42.7	
Early onset (≤35 years)	155	37.7	13	8.4	7	4.5	20	12.9	135	87.1
Bilateral breast cancer	46	11.2	4	8.7	5	10.9	9	19.6	37	80.4
Family history										
Breast cancer only	161	39.2	11	6.8	15	9.3	26	16.1	135	83.9
Ovarian cancer only	11	2.7	4	36.3	1	9.1	5	45.5	6	54.5
Both breast and ovarian cancer	8	1.9	1	12.5	2	25.0	3	37.5	5	62.5
No family history										
Early onset (≤35 years)	135	32.8	6	4.4	6	4.4	12	8.8	123	91.2
Bilateral breast cancer	30	7.3	2	6.7	1	3.3	3	10.0	27	90.0
Both breast and ovarian cancer	4	1.0	1	25.0	1	25.0	2	50.0	2	50.0
Multiple organ cancer, except ovarian cancer	14	3.4	0	0.0	0	0.0	0	0.0	14	100.0

TABLE II Univariate analysis of the immunohistologic features of basal-like breast cancer and *BRCA1/2* mutations

Feature and status		Overall (*n*)	*BRCA1*			*BRCA2*			Non-*BRCA*	
			(*n*)	(%)	*p* Value	(*n*)	(%)	*p* Value	(*n*)	(%)
CK5/6	Negative	143	6	4.2	0.002	11	7.7	0.299	126	88.1
	Positive	46	9	19.6		1	2.2		36	78.2
EGFR	Negative	199	10	5.0	0.020	17	8.5	0.082	172	86.5
	Positive	60	9	15.0		1	1.7		50	83.3
p53	Negative	292	15	5.1	0.209	22	7.5	0.054	255	87.4
	Positive	119	10	8.4		3	2.5		106	89.1
ER	Negative	136	20	14.7	<0.001	6	4.4	0.385	110	80.9
	Positive	275	5	1.8		19	6.9		251	91.3
PR	Negative	173	20	11.6	<0.001	10	5.8	0.827	143	82.6
	Positive	238	5	2.1		15	6.3		218	91.6
HER2	Negative	311	23	7.4	0.056	24	7.7	0.017	264	84.9
	Positive	97	2	2.1		1	1.0		94	96.9
TNBC	Negative	318	6	1.9	<0.001	19	6.0	0.866	293	92.1
	Positive	93	19	20.4		6	6.5		68	73.1

CK5/6 = cytokeratin 5/6; EGFR = epidermal growth factor receptor; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer.

BRCA1/2 mutation was also higher in patients with TNBC than in those with non-TNBC (14.6% vs. 4.9%, $p = 0.027$). The prevalence of *BRCA1* mutations was significantly higher in patients with TNBC than in those with non-TNBC (20.4% vs. 1.9%, $p < 0.001$), but the prevalence of *BRCA2* mutations was not different in patients with TNBC and with non-TNBC (6.5% vs. 6.0%, $p = 0.866$). When patients were divided by age group (younger and older than 35 years), the *BRCA1* mutation rate was higher in patients with TNBC than with non-TNBC in both age groups (Table IV); however, in the case of patients more than 35 years of age, the difference in prevalence between patients with TNBC and with non-TNBC was not statistically significant (13.3% vs. 1.2%, $p = 0.063$).

BRCA Mutation Rates According to PTEN Status in Patients with TNBC

Of the 68 patients tested for PTEN status, 37 (54.4%) were PTEN-negative, and 31 (45.6%) showed intact PTEN staining. The prevalence of *BRCA1* and *BRCA2* mutations did not differ by PTEN status (*BRCA1*: 18.9% vs. 25.8%, $p = 0.495$; *BRCA2*: 10.8% vs. 6.5%, $p = 0.684$). Similarly, the prevalence of *BRCA1* or *BRCA2* mutation did not differ between the groups when they were stratified by family history of breast or ovarian cancer (Table V).

DISCUSSION

In the present study, we evaluated the association between IHC features of breast cancer and *BRCA* mutation in a Korean population. We observed that, on univariate analysis, CK5/6, EGFR, ER, PR, and TNBC were associated with *BRCA1* mutation. However, on multivariate analysis, only TNBC was predictive of *BRCA1* mutation. No association between the basal-like phenotype and *BRCA2* mutation was observed.

Since the recognition that *BRCA1*-related breast cancer is similar to basal-like breast cancer, several studies have suggested that features of basal-like breast cancer might help to identify carriers of *BRCA1* mutations. Foulkes *et al.*[8] observed CK5/6 expression in 15 of 17 (88%) *BRCA1*-related breast cancers negative for ER and HER2, finding that expression of CK5/6 was associated with *BRCA1* mutation. However, their study was limited to Ashkenazi Jewish women, and only breast cancer specimens negative for ER and HER2 underwent immunostaining for CK5/6. In our study, CK5/6 was associated with *BRCA1* breast cancer on univariate analysis, but that association was not statistically significant on multivariate analysis. Lakhani and colleagues[12] compared 182 *BRCA1* carriers with 109 control subjects and evaluated cytokeratins (CK14, CK5/6, CK17), osteonectin, and EGFR expression as independent predictors of *BRCA1* mutation. They found that ER negativity and CK14 and CK5/6 expression were independent markers of *BRCA1* mutation, suggesting that cytokeratin staining and ER status, combined with a family history of breast or ovarian cancer, might more accurately predict the probability of carrying a *BRCA1* mutation. Collins *et al.*[16] reported that the expression of basal cytokeratins and EGFR could help to identify a subset of TNBC patients with a basal-like

TABLE III Multivariate analysis of the immunohistologic features of basal-like breast cancer and *BRCA1/2* mutation

Feature	*BRCA1*			*BRCA1/2*		
	OR	95% CI	*p* Value	OR	95% CI	*p* Value
CK5/6	1.909	0.357 to 10.195	0.450	1.469	0.360 to 5.986	0.592
EGFR	0.624	0.161 to 2.414	0.494	0.428	0.118 to 1.556	0.198
p53	0.682	0.192 to 2.425	0.555	0.496	0.169 to 1.450	0.200
TNBC	6.922	1.183 to 40.492	0.032	3.627	0.851 to 15.450	0.081

OR = odds ratio; CI = confidence interval; CK5/6 = cytokeratin 5/6; EGFR = epidermal growth factor receptor; TNBC = triple-negative breast cancer.

TABLE IV Comparison of *BRCA* mutation rates according to triple-negative breast cancer status

Characteristic	Triple negative status [*n* (%)]				Non–triple negative status [*n* (%)]				*p* Value for …		
	Pts	*BRCA1*	*BRCA2*	Total *BRCA*	Pts	*BRCA1*	*BRCA2*	Total *BRCA*	*BRCA1/2*	*BRCA1*	*BRCA2*
Overall cohort	93	19 (20.4)	6 (6.5)	25 (26.9)	318	6 (1.9)	19 (6.0)	25 (7.9)	<0.001	<0.001	0.866
With family history											
Early onset (≤35 years)	13	7 (53.9)	0 (0.0)	7 (53.9)	7	0 (0.0)	1 (14.3)	1 (14.3)	0.158	0.044	0.350
>35 Years	32	6 (18.8)	5 (15.6)	11 (34.4)	128	3 (2.3)	12 (9.4)	15 (11.7)	0.002	0.002	0.337
Total	45	13 (28.9)	5 (11.1)	18 (40.0)	135	3 (2.2)	13 (9.6)	16 (11.9)	<0.001	<0.001	0.777
Without family history											
Early onset (≤35 years)	33	4 (12.1)	1 (3.0)	5 (15.2)	102	2 (2.0)	5 (4.9)	7 (6.9)	0.165	0.031	1.000
>35 Years	15	2 (13.3)	0 (0.0)	2 (13.3)	81	1 (1.2)	1 (1.2)	2 (2.5)	0.114	0.063	1.000
Total	48	6 (12.5)	1 (2.1)	7 (14.6)	183	3 (1.6)	6 (3.3)	9 (4.9)	0.027	0.003	1.000

Pts = patients.

TABLE V Prevalence of *BRCA1/2* mutations by PTEN (phosphate and tensin homologue) status in patients with triple-negative breast cancer (TNBC)

PTEN status	*BRCA* status [*n* (%)]				*p* Value for …		
	All	*BRCA1*	*BRCA2*	Non-*BRCA*	*BRCA1/2*	*BRCA1*	*BRCA2*
All with TNBC	68	15 (22.1)	6 (14.7)	47 (69.1)	0.822	0.495	0.684
Loss	37	7 (18.9)	4 (10.8)	26 (70.3)			
Intact	31	8 (25.8)	2 (6.5)	21 (67.7)			
With family history	34	10 (29.4)	5 (14.7)	19 (55.9)	0.730	1.000	1.000
Loss	17	5 (29.4)	3 (17.6)	9 (53.0)			
Intact	17	5 (29.4)	2 (11.8)	10 (58.8)			
Without family history	34	5 (14.7)	1 (2.9)	28 (82.4)	0.672	0.627	1.000
Loss	20	2 (10.0)	1 (5.0)	17 (85.0)			
Intact	14	3 (21.4)	0 (0.0)	11 (78.6)			

Pts = patients.

phenotype, but was not sufficient to identify women with TNBC who were likely to carry a germline *BRCA1* mutation. Similarly, in our study, the basal-like phenotype was associated with *BRCA1* mutation, but TNBC was the only significant predictive variable on multivariate analysis.

Several studies have reported that loss of PTEN expression is significantly associated with basal-like breast cancer and *BRCA1*-associated hereditary breast cancer[13,15]. Phuah *et al.*[17] evaluated PTEN status for 26 TNBC patients and reported that the addition of 2 criteria (triple negativity and PTEN status) improved the sensitivity of the Manchester scoring method, suggesting that PTEN status could improve the identification of *BRCA1* mutation carriers. We therefore evaluated PTEN status in 68 TNBC patients and compared the prevalence of *BRCA1* mutations in the PTEN-intact and PTEN-negative groups. No difference between those groups was observed in our study. Whether loss of PTEN expression is associated with *BRCA1*-related breast cancer is still controversial, and further studies involving larger patient cohorts will be required to address this question.

Several studies have examined the prevalence of *BRCA* mutations in unselected TNBC patients[18–21], and their authors have suggested that TNBC patients should be considered for *BRCA1* and *BRCA2* genetic testing based on the evidence of high *BRCA* mutation prevalence in unselected TNBC patients. Muendlein *et al.*[18] assessed the prevalence of *BRCA* mutation in 100 unselected TNBC patients. They observed a 21% rate of *BRCA* mutation, and calculated that 38.1%–52.4% of *BRCA1/2* mutation carriers would be missed under the current German and Austrian national guidelines for genetic testing, which do not include TNBC as a genetic testing criterion. Villarreal-Garza *et al.*[19] investigated 190 unselected Mexican women with TNBC at the age of 50 years or younger. They found that the prevalence of *BRCA* mutations was 30.3% in women who were diagnosed at the age of 40 years or younger and 18.3% in those diagnosed between the ages of 41 and 50 years. Sharma *et al.*[20] reported that the prevalence of *BRCA* mutations was 15.4% in 207 unselected TNBC patients in a study that incorporated stratification by significant family history and age at diagnosis. In their multivariate model, the probability of a *BRCA* mutation in a patient with significant family history and diagnosis at age 51 was 29.5%, which was much higher than the 5.3% for a patient with no significant family history and diagnosis at age 51. Couch *et al.*[21] analyzed 1824 TNBC patients unselected for family history of breast or ovarian cancer and found that 14.6% of the overall group carried deleterious germline mutations, with 11.2% having mutations in *BRCA1* (8.5%) and *BRCA2* (2.7%). They also analyzed the prevalence of *BRCA* mutation by family history of cancer and age. With no family history of cancer, the prevalence of *BRCA1/2* mutation was 19.8%, 15.4%, 8.6%, 7.5%, and 1.4% in patients diagnosed at less than 35 years of age, 35–39 years of age, 40–49 years of age, 50–59 years of age, and more than 60 years of age respectively.

Although the prevalence of *BRCA* mutation was high for unselected TNBC patients in most studies, those studies included high-risk subjects with a significant family history and early-onset breast cancer, which could result in an overestimation of the *BRCA* mutation prevalence. The identification of *BRCA* mutations in TNBC patients can have a significant effect on treatment. Compared with patients having other breast cancer subtypes, those with TNBC often have a worse prognosis[22], and no suitable targeted therapy has been developed for TNBC patients. However, the pathologic complete response rate reached 83% after cisplatin neoadjuvant chemotherapy in patients with *BRCA1*-related breast cancer[23]. Moreover, in carriers of *BRCA1* or *BRCA2* mutations, treatment with inhibitors of PARP (poly ADP ribose polymerase) has shown antitumour activity, leading to synthetic lethality in tumour cells[24]. Thus, the *BRCA* mutation status of patients with TNBC might be a predictor of response to those therapies.

Based on recent studies, it therefore seemed important to identify whether TNBC should be incorporated into Korean genetic testing criteria. In the present study, we found that TNBC is an independent predictor of *BRCA1* mutation in patients at high risk of hereditary breast and ovarian cancer. Given a positive family history, the *BRCA1* mutation rate was much higher in patients with TNBC than in those with non-TNBC (28.9% vs. 2.2%, $p < 0.001$). Even in TNBC patients more than 35 years of age with no family history, the *BRCA1* mutation rate was more than 10%. Nevertheless, their mutation rate was not statistically significantly different from the rate for their non-TNBC counterparts (13.3% vs. 1.2%,

$p = 0.063$). Our results suggest that TNBC might play an important role in stratifying a patient's risk of having a *BRCA1* mutation, especially for patients with a family history of breast or ovarian cancer, or with early-onset breast cancer.

Our study has several limitations. First, in this single-institution study, the patient population was relatively small. The results might have differed if the study population had been larger. Second, the study was somewhat focused on high-risk patients, representing a possible selection bias. Lastly, IHC results for some patients, such as those for CK5/6 and EGFR, were missing.

CONCLUSIONS

In patients at high risk of hereditary breast and ovarian cancer, TNBC is an independent predictor for *BRCA1* mutation. Other IHC features of basal-like breast cancer did not improve the predictive estimates for *BRCA1* mutation risk. More research is required to identify the subset of women who are at a greater risk of carrying a *BRCA1* mutation.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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