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ORIGINAL REPORT

Effect of Short-Term Hormone Replacement Therapy on Breast Cancer Risk Reduction After Bilateral Prophylactic Oophorectomy in *BRCA1* and *BRCA2* Mutation Carriers: The PROSE Study Group

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ABSTRACT

Purpose
Bilateral prophylactic oophorectomy (BPO) is widely used for cancer risk reduction in women with *BRCA1/2* mutations. Many premenopausal women choose to take hormone replacement therapy (HRT) after undergoing BPO to abrogate immediate symptoms of surgically-induced menopause. Thus, we evaluated whether the breast cancer risk reduction conferred by BPO in *BRCA1/2* mutation carriers is altered by use of post-BPO HRT.

Methods
We identified a prospective cohort of 462 women with disease-associated germline *BRCA1/2* mutations at 13 medical centers to evaluate breast cancer risk after BPO with and without HRT. We determined the incidence of breast cancer in 155 women who had undergone BPO and in 307 women who had not undergone BPO on whom we had complete information on HRT use. Postoperative follow-up was 3.6 years.

Results
Consistent with previous reports, BPO was significantly associated with breast cancer risk reduction overall (hazard ratio [HR] = 0.40; 95%CI, 0.18 to 0.92). Using mutation carriers without BPO or HRT as the referent group, HRT of any type after BPO did not significantly alter the reduction in breast cancer risk associated with BPO (HR = 0.37; 95% CI, 0.14 to 0.96).

Conclusion
Short-term HRT use does not negate the protective effect of BPO on subsequent breast cancer risk in *BRCA1/2* mutation carriers.

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INTRODUCTION

Women with germline *BRCA1* or *BRCA2* (*BRCA1/2*) mutations have a markedly increased risk of breast and ovarian cancer compared with the general population.[1-4] Because effective screening for ovarian cancer is currently not available, these women are advised to undergo bilateral prophylactic oophorectomy (BPO) after childbearing, an intervention that reduces the risk of ovarian cancer by approximately 90%.[5,6] BPO also reduces breast cancer risk by 50% or more in *BRCA1/2* mutation carriers and genetically uncharacterized women.[7-10]

An immediate consequence of BPO in premenopausal women is the induction of surgical menopause. Surgical menopause in young women can result in severe hot flashes, vaginal dryness, sexual dysfunction, sleep disturbances, and cognitive changes that may affect quality of life.[11] As a result,

many premenopausal women who undergo BPO elect to use at least short-term hormone replacement therapy (HRT) to alleviate these symptoms. In addition, some premenopausal women may defer BPO because of concerns about HRT and breast cancer risk, while remaining at high risk for ovarian cancer. Because there are multiple studies suggesting that HRT, particularly combined with estrogen-progesterone use, increases risk of breast cancer,[12] there is legitimate concern that HRT may offset the breast cancer risk reduction conferred by BPO.

To date, the effect of HRT on post-BPO breast cancer risk reduction in *BRCA1/2* mutation carriers has not been conclusively determined. Using a cohort of women with *BRCA1/2* mutations, we reported[10] that ever/never use of any HRT was not a significant independent predictor of breast cancer outcome in a multivariate Cox model that included BPO. In a subsequent study, we reported that exclusion of women with HRT exposure after BPO did not significantly affect the magnitude of breast cancer risk reduction.[5] However, the sample set on which we had complete HRT data was small and thus, the confidence intervals on these estimates were large. While these data suggested that short-term HRT use does not negate the breast cancer risk reduction conferred by BPO, the strength of these prior observations are insufficient to guide clinical practice.

METHODS

Sampling Design

Women with germline, disease-associated *BRCA1/2* mutations, who had BPO of any type, were identified from 13 North American and European centers (ie, Medical Univeristy of Vienna, Creighton University, Dana-Farber Cancer Institute, Fox Chase Cancer Center, Georgetown University, University of Chicago, University of Pennsylvania, University of Utah, Netherlands Cancer Institute, Royal Marsden Hospital, St Mary's Hospital, University of Texas-Southwestern, and Yale University). The *BRCA1/2* mutation status of all subjects was confirmed by direct mutation testing with full informed consent under protocols approved by the human subjects review boards at each institution. Women with *BRCA1/2* variants of unknown functional significance were excluded.

To evaluate whether HRT influences breast cancer risk after BPO while considering possible sources of bias in ascertainment and data collection, we constructed a prospective sample generated from the cohort of *BRCA1/2* mutation carriers described above, using the recommendations of Klaren et al,[13] Hartmann et al,[14] and Wacholder.[15] These recommendations were made specifically to address potential sampling and information biases in studies of prophylactic surgery from multicenter cohorts.

BPO cases were women with a disease-associated *BRCA1/2* mutation who underwent BPO. BPO cases were excluded if they reported BPO before center ascertainment or if they reported a breast or ovarian cancer diagnosis before or within 6 months of center ascertainment. Women were also excluded as BPO cases if they had had a history of ovarian cancer (including borderline tumors and tumors of low malignant potential) before BPO, if they had undergone unilateral or bilateral mastectomy before BPO, or had a personal history of breast cancer (including in situ carcinoma) at or before the time of their BPO. Women were included only if BPO was not performed to treat ovarian cancer. Women were also excluded as BPO cases if they used HRT before BPO.

Women without BPO (non-BPO controls) were eligible if they had a disease-associated *BRCA1/2* mutation, were alive with at least one ovary intact, and had no history of ovarian cancer at or before center ascertainment. Controls were excluded if they had undergone unilateral or bilateral mastectomy or had a history of breast or ovarian cancer at, before, or within 6 months of center ascertainment. Using these criteria, we identified 155 BPO patient cases and 307 non-BPO patient controls, all of whom had disease-associated *BRCA1/2* mutations. Sixteen of 155 BPO patient cases (10.3%) underwent BPO after age 50. There is also overlap between the participants in the present data set and that of our previous publication,[6] but these two data sets are not identical because (1) additional participants were recruited between the publication of our earlier paper and the present paper, and (2) different inclusion/exclusion criteria were applied in the two articles.

Data Collection

Entry and follow-up of study participants at each center were undertaken without regard to surgical status. Vital status and cancer history were obtained using medical records, telephone interviews, and/or self-administered questionnaires. For women who had died after entry into the study, we reviewed medical records and family history reports to establish cancer diagnoses and verify vital status. Self-reported reproductive and exposure history, including hormone use, smoking, and alcohol consumption were obtained by questionnaire.

Specific information collected regarding HRT use included ever/never HRT use, the year a participant started and stopped taking HRT, total months of use, reason for taking HRT, type of HRT (ie, estrogen, progesterone, both, or other), name brand of supplement, mode of HRT administration (ie, oral, patch, vaginal), and reason for stopping HRT use, if applicable. Information regarding more than one exposure to HRT was also collected. HRT duration was calculated as reported or as the time from the year HRT use began until a breast cancer or other censoring event. Women who started using HRT for the first time after a breast cancer diagnosis or other censoring event were considered non-HRT users. In BPO patient cases, HRT use was considered from the time of BPO until a breast cancer diagnosis or other censoring event occurred.

BPO and cancer diagnoses were verified by review of medical records, operative notes, and/or pathology reports. Specific information collected regarding prophylactic surgeries included type of ovarian surgery, removal of fallopian tubes, and reason for surgery. Breast cancer characteristics identified included histologic type and grade, TNM stage, and mode of detection.

Statistical Analysis

Cox proportional hazards models were used to estimate differences in cancer incidence by BPO status using STATA version 8.0 (STATA Corporation, College Station, TX). A robust variance-covariance estimation method was used to correct for nonindependence of observations among subjects from the same family or within centers. Potential confounders including age, parity, *BRCA1* versus *BRCA2* mutation, and center were adjusted for in a multivariate Cox regression model.

BPO subjects were followed from time of BPO. In our primary analysis, non-BPO patient controls were followed from the date of center ascertainment or genetic testing (if testing preceded center ascertainment) until first breast cancer diagnosis or other censoring event. In a secondary analysis, non-BPO patient controls were followed from the time of center ascertainment, if they underwent genetic testing before the time they were ascertained. However, this second analysis has the potential to induce bias because non-BPO patient controls who were tested and subsequently diagnosed with ovarian cancer before center ascertainment may not be included in our analysis. Therefore, excluding follow-up time in non-BPO patient controls between genetic testing and study ascertainment could result in overestimating the associated risk reduction effect. Therefore, follow-up time from date of genetic testing in non-BPO patient controls was selected to provide a more conservative estimate of risk reduction.

The primary end point of interest was the first diagnosis of in situ (ductal) or invasive breast cancer. Ductal carcinoma-in-situ was included in the analysis as it is thought to be a precursor lesion for invasive breast cancer, thus, subject to the same risk exposures. Study patients were censored at the date of ovarian or primary peritoneal carcinoma diagnosis, prophylactic mastectomy, death, or date of last contact if none of these other events occurred.

RESULTS

Significant differences were observed between women who underwent BPO versus non-BPO patient controls in terms of birth year, use of HRT, parity, and smoking history (Table 1), as well as number of breast cancers, mean age at breast cancer diagnosis, and years of follow-up to censoring (Table 2). Most of these factors reflect the use of BPO or the consequences of this surgery. For example, BPO patient cases were significantly more likely than non-BPO patient controls to have ever taken HRT (60% *v* 7%; $P < .001$) because premenopausal women with intact ovaries are unlikely to require HRT for symptom management. BPO patient cases and non-BPO patient controls did not differ with respect to oral contraceptive use or probability of having a *BRCA1* versus *BRCA2* mutation. BPO patient cases were significantly older than non-BPO patient controls (42.7 years *v* 35.0 years; $P < .001$). Therefore, to account for potential confounders, all analyses were adjusted for year of birth, *BRCA1* versus *BRCA2* mutation, center of ascertainment, and parity. BPO patient cases were followed for an average of 2.6 years. Non-BPO patient controls were followed for an average of 4.1 years. Twenty-five of 155 BPO patient cases (16%) and 102 of 307 non-BPO patient controls (33%) were followed for at least 5 years.

Only the first primary breast cancer was considered in the risk reduction analyses. However, a second primary breast cancer developed in six subjects (all were non-BPO patient controls). Twelve of 155 BPO patients (8%) and 65 of 307 non-BPO patient controls (21%) were diagnosed with a first primary breast cancer during follow-up (HR = 0.40; 95% CI, 0.18 to 0.91). Furthermore, women who underwent BPO were diagnosed with breast cancer later than non-BPO patient controls (mean age at diagnosis 45.6 years and 39.3 years, respectively). The median time until diagnosis for BPO patients was 2.0 years (range, 0.8 to 5.8 years). For non-BPO patient controls, median time to diagnosis was 3.7 years (range, 0.5 to 12.9 years).

One hundred fourteen women (25%) used some form of HRT, including 93 of 155 BPO patients (60%) and 21 of 307 non-BPO patient controls (7%). Table 3 describes the risk of breast cancer after BPO with and without HRT use compared with women who did not have BPO and did not take any HRT. The reduction in breast cancer risk associated with BPO was not different in women who had taken HRT (HR = 0.37; 95% CI, 0.14 to 0.96) than in the overall

Table 1. Study Subject Characteristics

Variable	No.	*P**
Total sample with *BRCA1/2* mutations	462	
BPO patient cases	155	
Non-BPO patient controls	307	
Birth year		< .001
BPO patient cases		
Mean	1956	
Range	1927-1968	
Non-BPO patient controls		
Mean	1961	
Range	1916-1982	
Hormone replacement therapy use		< .001
BPO patient cases	93	
%	60	
Non-BPO patient controls	21	
%	7%	
Parity		.001
BPO patient cases	136	
%	88	
Non-BPO patient controls	234	
%	76	
Number of live births		.001
BPO patient cases		
Mean	2.5	
Range	1-7	
Non-BPO patient controls		
Mean	2.2	
Range	1-6	
Ever user of oral contraceptives		.41
BPO patient cases	123	
%	79	
Non-BPO patient controls	249	
%	81	
Ever smoker		.04
BPO patient cases	50	
%	32	
Non-BPO patient controls	129	
%	42%	

Abbreviation: BPO, bilateral prophylactic oophorectomy.
*Comparison of BPO patient cases and non-BPO patient controls was performed using Fisher's Exact Test (for discrete variables) or Wilcoxon rank sum test (for continuous variables).

Table 2. Surgical Status and Cancer Diagnoses in the Study Sample

Variable	No.	P*
Age at BPO, years		
Mean	42.7	
Range	21.5-73.9	
Breast cancer diagnosis		.001
BPO patient cases	12	
%	8	
Non-BPO patient controls	65	
%	21	
Age at breast cancer diagnosis, years		< .001
BPO patient cases		
Mean	45.6	
Range	33.1-71.2	
Non-BPO patient controls		
Mean	39.3	
Range	27.6-52.0	
Years of follow-up to diagnosis		.13
BPO patient cases		
Mean	2.9	
Range	0.8-5.8	
Non-BPO patient controls		
Mean	4.3	
Range	0.5-12.9	
Years of follow-up to censoring†		< .001
BPO patient cases		
Mean	2.6	
Range	0.1-19.1	
Non-BPO patient controls		
Mean	4.1	
Range	0.1-18.8	
BRCA1 mutation		.4
BPO patient cases	110	
%	71	
Non-BPO patient controls	205	
%	67	

Abbreviation: BPO, bilateral prophylactic oophorectomy.
* Comparison of BPO patient cases and non-BPO patient controls was performed using Fisher's Exact Test (for discrete variables) or Wilcoxon rank sum test (for continuous variables).
†Includes death or date of last contact.

cohort. One hundred thirty-nine BPO patients (90%) had their surgery before the age of 50. Eighty-nine of these women (64%) used some form of HRT, while 50 women (36%) did not. In the sample, HRT use among BPO patients did not significantly alter postsurgical breast risk (HR = 1.35; 95% CI, 0.16 to 11.58).

As recent data suggest, progesterone use confers a substantial portion of the increased breast cancer risk associated with HRT,[16] we examined the effect of progesterone with or without estrogen on post-BPO breast cancer risk reduction (Table 3). Of the 93 BPO patient cases (60%) who took HRT, 54 patients (58%) took estrogen only, 34 patients (22%) took progesterone with or without estrogen, and five patients did not specify HRT type. Breast cancer risk reduction among BPO patient cases who took progesterone with or without estrogen versus BPO patient cases who took estrogen alone was not significant (HR = 2.56; 95% CI, 0.08 to 78.13 for combined therapy), however, the small number of women who took combined HRT limited the power to detect a meaningful effect in this subgroup.

DISCUSSION

In this cohort of women with *BRCA1/2* mutations, short-term HRT following BPO did not alter the substantial and significant reduction in breast cancer risk associated with BPO during the available follow-up period. In fact, women who had undergone BPO and took HRT had approximately a third the risk of developing breast cancer as women who had not undergone BPO and did not take HRT. Among women who underwent BPO, there was no significant increase in post-BPO breast cancer risk among women who took short-term HRT, but a substantially larger sample will be required for a formal analysis of interaction between HRT and BPO. More power is also necessary to examine effects of specific preparations of HRT used (ie, estrogen *v* estrogen plus progesterone), as well as the specific BPO procedure (eg, bilateral salpingo-oopherectomy [BSO] *v* total abdominal hysterectomy [TAH] with BSO). However, a prospective randomized trial of HRT after BPO in women with *BRCA1/2* mutations would likely be impossible to conduct. Therefore, while longer follow-up of this cohort is essential to assess long-term effects of post-BPO HRT use, these data provide valuable information for premenopausal women facing BPO.

The relationship between HRT and breast cancer risk reduction associated with BPO is important for several reasons. Because as many as 90% of women with *BRCA1/2* mutations will develop breast or ovarian cancer over their lifetime in the absence of intervention, adoption of effective cancer risk reduction interventions is critical. Although BPO substantially reduces the risk of breast and ovarian cancer in these high risk women,[5,6] concerns about surgical menopause may dissuade women from undergoing premenopausal BPO, limiting the impact of this intervention on the burden of cancer among *BRCA1/2* mutation carriers. Results of the current study suggest that women with *BRCA1/2* mutations will reduce their risk of breast cancer through BPO irrespective of their subsequent decision about HRT, at least in the short term. Thus, women with *BRCA1/2* mutations should not defer BPO, which may save their lives because of concerns about the immediate impact of menopausal symptoms on their quality of life. This is important information that should facilitate the decision to undergo BPO after the completion of childbearing and reduce the incidence of breast and ovarian cancer among women with *BRCA1/2* mutations.

Although our sample size and current follow-up did not allow us to examine the duration of hormone use, many

Table 3. Breast Cancer Risk Reduction After BPO Stratified by Postsurgical HRT Use

Variable		Total Sample			BPO Before Age 50		
		No.	HR	95% CI*	No.	HR	95% CI*
No surgery	No HRT	286	1.0	—	286	1.0	—
BPO	No HRT	62	0.38	0.09 to 1.59	50	0.59	0.14 to 2.52
BPO	Any HRT	93	0.37	0.14 to 0.96	89	0.30	0.11 to 0.85
BPO	E2 only	50	0.44	0.12 to 1.61	50	0.44	0.12 to 1.61
BPO	PROG ± E2	34	0.43	0.07 to 2.68	34	0.43	0.07 to 2.68

Abbreviations: BPO, bilateral prophylactic oophorectomy; HRT, hormone replacement therapy; HR, hazard ratio; E2, estrogen; PROG, progesterone.
*Adjusted for birth year, *BRCA1* versus *BRCA2*, center of ascertainment, and parity.

women who undergo premenopausal BPO take HRT only until the age when they would have experienced natural menopause, generally age 50. Thus, this study lends support to the hypothesis that short-term use of hormone replacement titrated to manage immediate postoperative menopausal symptoms may have different implications for breast cancer risk than long-term hormone exposure in postmenopausal women.[17] Furthermore, these results extend the findings of a recent decision analysis using hormone-associated risk data from the recently published Women's Health Initiative (WHI),[16,18] which suggests that short-term use of HRT after premenopausal BPO is associated with little change in life expectancy, whereas the impact of long-term use after age 50 was more substantial.[19]

Another important aspect of decision making about HRT is the relative benefits and risks of estrogen alone versus combined therapy with estrogen and progesterone. This decision has implications for the use of TAH at the time of BPO, as use of unopposed estrogen in the absence of hysterectomy is associated with an increased risk of endometrial cancer.[20] Recent data from the WHI demonstrated a significantly increased risk of breast cancer among postmenopausal women who took estrogen and progesterone, but not among women who took estrogen alone.[16,18] This difference is also supported by the results of the Million Women Study, which found a two-fold increase in breast cancer risk for use of estrogen and progesterone (relative risk [RR] = 2.00; 95% CI, 1.89 to 2.12) but a significantly lower risk for users of estrogen alone (RR = 1.30; 95% CI, 1.21 to 1.40).[21] In the current analysis, the degree of breast cancer risk reduction from BPO was not significantly different between women who took only estrogen and women who took both estrogen and progesterone. However, the precision of our assessment of the effect of estrogen and progesterone on the breast cancer risk reduction from BPO is limited by the small number of women who took both estrogen and progesterone (N = 34) and the relatively short length of follow-up and duration of HRT use (mean, 3.2 years). However, on the basis of the risk of estrogen and progesterone in the Million Women Study, and the difference in the effect of estrogen alone compared with estrogen and progesterone in the WHI,[16,21] the addition of progesterone remains a concern.

Therefore, women may wish to weigh the risks and benefits of TAH at time of BPO using the following considerations. First, TAH allows women to use unopposed estrogen replacement therapy rather than combined estrogen plus progesterone replacement therapy to minimize potential breast cancer risk and eliminate the endometrial cancer risk associated with unopposed estrogen exposure. Second, The Breast Cancer Linkage Consortium reported an increased risk of uterine (RR = 2.65) and cervical cancer (RR = 3.72) in *BRCA1* mutation carriers, particularly in women younger than 65,[22] and other reports suggest an increased uterine cancer risk in *BRCA1/2* mutation carriers as well.[23-25] Even though early detection of these cancers is often possible and there in uncertainty whether women with *BRCA1/2* mutations are at increased uterine cancer risk, women already planning to undergo BPO may consider whether they wish to eliminate uterine cancer risks by undergoing TAH at the time of their BPO. Third, tamoxifen has been shown to decrease the risk of contralateral breast cancer in *BRCA1*/2 mutation carriers.[26] Therefore, tamoxifen use for prevention of breast cancer is a consideration for *BRCA1/2* mutation carriers. The reported increased uterine cancer risk associated with tamoxifen[27] is an additional consideration for women contemplating TAH. Fourth, there is a known 100-fold excess risk of fallopian tube carcinoma in *BRCA1/2* mutation carriers compared with the general population.[4] Because a remnant of the fallopian tube is left in the uterine wall at the time of BSO without TAH, there is a theoretical benefit in considering TAH. However, there is currently little information about the occurrence of fallopian tube cancer among women who have undergone BPO without TAH.

However, if women consider having TAH in addition to BPO, the added risk and recovery time from TAH should be considered. BPO is an acceptable option in part because surgical risks and recovery time are outweighed by the benefit of a marked breast and ovarian cancer risk reduction. However, the risk benefit ratio for TAH in addition to BPO is more complex, both because of the small absolute

advantages of TAH and the potential for slightly higher morbidity associated with this procedure. All of these elements must be factored into the patient's decision about surgical approach to cancer risk reduction. Thus, other practices identified by the coauthors if this article in the United States and Europe are known to include (1) BPO alone with combined estrogen/progesterone replacement; (2) BPO alone with short-term estrogen only replacement, considering the potential for increased risk of uterine cancer,[28] and (3) BPO alone with consideration of hysterectomy at a later time. These decisions are highly individual to the patient and should be made after weighing the risks and benefits to each woman.

Extricating the true effect of prophylactic surgery on cancer risk from observational data is challenging. Studies that employ multicenter cohorts of referral patients to assess the effect of prophylactic surgery have been criticized because of potential sources of sampling or information biases, including confounding by indication or the influence of competing events.[13-15] To minimize the potential for bias, we used a prospective sampling design by following the recommendations of Klaren et al,[13] Hartmann et al,[14] and Wacholder[15] in our primary analysis. However, we conducted an additional matched analysis to assess the robustness of our results. The results were the same as the overall analysis, providing further evidence that the breast cancer risk reduction associated with BPO persists in the setting of post-BPO HRT use. Furthermore, our results were similar in secondary analyses that counted follow-up time among non-BPO patient controls from the date of clinic ascertainment if they underwent genetic testing before center ascertainment. We hypothesized that this follow-up design could lead to biases away from the null hypothesis in terms of post-BPO breast cancer risk reduction. However, the hazard ratio estimates obtained from this secondary analysis (results not shown) did not differ from those reported in the primary analyses.

This study has several limitations. Although our analyses used one of the largest existing cohorts of women with *BRCA1/2* mutations, the sample provided insufficient power to detect effects for some comparisons. For example, HRT use is strongly correlated with having undergone BPO; thus, it was not possible to formally test the interaction between HRT and BPO. In addition, while the difference in magnitude of breast cancer risk reduction associated with BPO between women who did not take HRT, women who took estrogen and progesterone, and women who took estrogen only is intriguing, the small numbers of women in the first two groups limit the precision of the estimates and prevent any definitive conclusions about these comparisons. Similarly, timing of BPO use relative to age or natural menopausal status and the relationship of these events with HRT use could not be addressed because of small sample size.

In summary, BPO is an important cancer risk reduction management strategy for women with *BRCA1/2* mutations. On the basis of the results of the current study and WHI data on the use of estrogen alone for HRT, women with *BRCA1/2* mutations should be discouraged from deferring BPO because of fear of symptoms related to surgical menopause and should be reassured that use of short-term hormone replacement, if needed to manage menopausal symptoms, does not negate the breast cancer risk reduction from BPO.

Appendix

The PROSE (Prevention and Observation of Surgical Endpoints) Study Group: Baylor-Charles A. Sammons Cancer Center: Joanne L. Blum, MD, PhD, Becky Althaus, RN, PhD, CGC, Gabrielle Ethington; Beth Israel-Deaconess Medical Center: Nadine Tung, MD; Creighton University: Carrie Snyder, BA, Henry T. Lynch, MD, Patrice Watson, PhD; Dana-Farber Cancer Institute: Judy E. Garber, MD, MPH, Shelly McCormick; Fox Chase Cancer Center: Mary B. Daly, MD, PhD; Georgetown University: Camille Corio, Florence Felix, Claudine Isaacs, MD; Netherlands Cancer Institute: Matti Rookus, PhD, Marc van Beurden MD, PhD, Laura van ′t Veer, PhD; Royal Marsden Hospital: Rosalind Eeles, MD, Katherine Bishop; St. Mary's Hospital: D. Gareth Evans, MD, Fiona Lalloo, Andrew Shenton; University of Chicago: Shelly Cummings, Olofunmilayo Olopade, MD, Marjorie Roark; University of California, Irvine: Susan L. Neuhausen, PhD, Linda Steele; University of Pennsylvania: Tara Friebel, MPH, Timothy Rebbeck, PhD, Barbara Weber, MD; University of Texas Southwestern Medical Center: David Euhus, MD, Gail Tomlinson, MD, PhD; Medical University of Vienna: Theresa Wagner, PhD; Women's College Hospital: Steven A. Narod, MD, Kelly Metcalfe, PhD; Yale University: Ellen Matloff, MS

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