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Article

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Bilateral Oophorectomy and Breast Cancer Risk in *BRCA1* and *BRCA2* Mutation Carriers

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Abstract

Background: Whether oophorectomy reduces breast cancer risk among *BRCA* mutation carriers is a matter of debate. We undertook a prospective analysis of bilateral oophorectomy and breast cancer risk in *BRCA* mutation carriers.
Methods: Subjects had no history of cancer, had both breasts intact, and had information on oophorectomy status (n = 3722). Women were followed until breast cancer diagnosis, prophylactic bilateral mastectomy, or death. A Cox regression model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of breast cancer associated with oophorectomy (coded as a time-dependent variable). All statistical tests were two-sided.
Results: Over a mean follow-up of 5.6 years, 350 new breast cancers were diagnosed. Among women with a *BRCA1* or *BRCA2* mutation, oophorectomy was not associated with breast cancer risk compared with women who did not undergo an oophorectomy. The age-adjusted hazard ratio associated with oophorectomy was 0.96 (95% CI = 0.73 to 1.26, $P = .76$) for *BRCA1* and was 0.65 (95% CI = 0.37 to 1.16, $P = .14$) for *BRCA2* mutation carriers. In stratified analyses, the effect of oophorectomy was statistically significant for breast cancer in *BRCA2* mutation carriers diagnosed prior to age 50 years (age-adjusted HR = 0.18, 95% CI = 0.05 to 0.63, $P = .007$). Oophorectomy was not associated with risk of breast cancer prior to age 50 years among *BRCA1* mutation carriers (age-adjusted HR = 0.79, 95% CI = 0.55 to 1.13, $P = .51$).
Conclusions: Findings from this large prospective study support a role of oophorectomy for the prevention of premenopausal breast cancer in *BRCA2*, but not *BRCA1* mutation carriers. These findings warrant further evaluation.

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Whether or not bilateral oophorectomy reduces breast cancer risk among women with a BRCA1 or BRCA2 mutation continues to be a matter of debate (1). Recently, a prospective study from the Netherlands, which included 822 BRCA mutation carriers with a median follow-up of three years, showed no protective effect of oophorectomy on breast cancer risk (hazard ratio [HR] = 1.0, 95% confidence interval [CI] = 0.67 to 1.77) (1). The authors concluded that previous reports of a beneficial effect of oophorectomy for breast cancer risk reduction were spurious and could be attributed to various biases. The null effect reported in the Netherlands contrasts with the meta-analysis by Rebbeck et al., who reported a 51% (95% CI = 0.37 to 0.65) highly statistically significant reduction in breast cancer risk with bilateral oophorectomy for both BRCA1 and BRCA2 mutation carriers (2). The meta-analysis included both case-control and prospective studies, with sample sizes ranging from 597 to 988 women. In a case-control study of 1439 pairs of BRCA mutation carriers, we reported a statistically significant 54% reduction in breast cancer risk associated with oophorectomy (95% CI = 0.32 to 0.65) (3).

Oophorectomy is routinely recommended to healthy women with a BRCA mutation at age 35 years or thereafter to prevent cancers of the ovary, fallopian tube, or peritoneum and to reduce all-cause mortality (4,5). Also, among BRCA carriers with a previous diagnosis of breast cancer, oophorectomy statistically significantly reduces breast cancer mortality and decreases the risk of contralateral breast cancer (6,7). Given the negative consequences associated with surgical menopause, including climacteric symptoms, as well as possible adverse effects on cognition, bone density, and cardiac health, it is important that we clarify the impact of oophorectomy (and timing of surgery) on breast cancer risk (8).

Given the concerns regarding the methods of the case-control studies conducted to date, we undertook a prospective analysis of bilateral oophorectomy and breast cancer risk in 3722 BRCA mutation carriers with no history of cancer prior to study enrollment. Subjects were observed from the date of ascertainment until the date of last follow-up. We also evaluated the association of oophorectomy and breast cancer risk by BRCA mutation type, by age at diagnosis, and by estrogen receptor status of the tumor.

Methods

Study Population

Eligible study subjects included women who were enrolled in a prospective cohort study of deleterious BRCA1 and BRCA2 mutation carriers and were identified from 78 participating centers in 12 countries. All subjects had sought testing for BRCA1 and BRCA2 mutations because of a personal or family history of breast and/or ovarian cancer. All study subjects (with the exception of some from the University of Utah and University of California Irvine) received genetic counseling. The institutional review boards of the host institutions approved the study. All subjects provided written informed consent. Mutation detection was performed using a range of techniques, but all nucleotide sequences were confirmed by direct sequencing of DNA.

Data Collection

All subjects completed a baseline questionnaire at the individual center at the time of a clinic appointment or at their home at a later date. Follow-up questionnaires were completed every two years thereafter. These were either mailed to each participant to complete and return, or were administered over the phone by a genetic counselor or research assistant. The questionnaires requested information on family and personal history of cancer, and reproductive and medical histories, including preventive oophorectomy and mastectomy. Women were classified as having a bilateral oophorectomy if both ovaries were removed (with or without fallopian tubes or uterus intact). Women with a unilateral oophorectomy were included in the no-oophorectomy group. Information on incident breast cancers, including hormone receptor status, was collected from the follow-up questionnaires, and pathology records were reviewed. For this analysis, incident breast cancers consisted of first primary invasive breast cancers.

Study Subjects Available for Analysis

Women were eligible for the study if they completed at least one follow-up questionnaire. Of the 12 794 women who were initially eligible, we excluded women who had a prior diagnosis of breast cancer (n = 6307), ovarian cancer (n = 1546), or other cancer (n = 625), who had undergone a prophylactic bilateral mastectomy at baseline (n = 342), who were missing information on mastectomy status (n = 221), or who were missing age at menarche (n = 5). We excluded an additional 26 women who had a cancer diagnosis (n = 20), prophylactic mastectomy (n = 3), or completed a follow-up questionnaire (n = 3) prior to receipt of their genetic test results. After these exclusions, a total of 3722 subjects qualified for inclusion in the analysis. Among the 3722 subjects, 1974 (53%) completed their baseline questionnaire within a year of receiving genetic test results, 960 (26%) completed their baseline questionnaire more than one year following receipt of genetic testing, and 788 (21%) were missing information on the date of receipt of genetic testing.

Statistical Analysis

We compared women with and without oophorectomy for several variables. For continues variables, the values were compared using a *t* test. For categorical variables, we compared counts using a Chi-squared test. We estimated the annual breast cancer incidence (%) by calculating the total person-years for the entire cohort and the number of incident cases in the entire follow-up period. Incidence (%) was estimated as the ratio of the number of breast cancer cases to the total number of person-years.

We used a Cox regression model to estimate the hazard ratios and 95% confidence intervals of breast cancer associated with a bilateral oophorectomy. Bilateral oophorectomy was coded as a time-dependent variable. If a woman had a bilateral oophorectomy after the completion of the baseline questionnaire (or at any point in the follow-up), the exposure was updated to reflect the change in oophorectomy status. Participants were followed from the date of ascertainment (ie, date of genetic testing or date of baseline questionnaire, whichever was later; however, if date of genetic testing was missing, then the subjects were followed from the date of questionnaire completion) until either the: 1) date of completion of the last follow-up questionnaire, 2) date of breast cancer diagnosis, 3) date of prophylactic bilateral mastectomy, 4) date of ovarian cancer diagnosis, or 5) date of death. In the multivariable models, we adjusted for age at baseline (<40, 40–49, ≥50 years),

family history of breast cancer (0, 1, 2, ≥3 affected first-degree relatives), country of residence (Poland, Canada, United States, other) oral contraceptive use (ever/never), age at menarche (≤12, 13, ≥14 years), parity (0, 1, 2, 3, ≥4 children), and breastfeeding (ever/never). We also performed analyses stratified by BRCA mutation type, estrogen receptor status of the tumor, and excluding women with an oophorectomy at or prior to the baseline questionnaire, as well as analyses censoring at different ages.

All analyses were performed using the SAS statistical package, version 9.1.3 (SAS Institute, Cary, NC). All *P* values were based on two-sided tests and were considered statistically significant if .05 or lower.

Results

There were 3722 women with a BRCA1 or BRCA2 mutation included in the current analysis. The baseline characteristics are summarized in Table 1; 1552 women had a bilateral oophorectomy either before (n = 857) or after (n = 695) study enrollment, and 2170 women did not have an oophorectomy. Many of the variables differed between the two exposure groups, but this was likely a reflection of the mean age at study entry in the oophorectomy group (33.4 vs 46.2 years, $P < .001$). On average, compared with women with both ovaries intact, women with an oophorectomy were older, parous, had breastfed, had used oral contraceptives, and had a stronger family history of breast cancer ($P < .001$).

Over a mean follow-up of 5.6 years (range = 0–21.2 years), 350 new first primary breast cancers were diagnosed in the entire cohort; of these, 143 (40.9%) had an oophorectomy prior to the diagnosis of breast cancer. The total number of person-years, number of incident breast cancers, and annual incidence among all the study subjects, combined and stratified by age, oophorectomy status, and BRCA mutation type, are displayed in Table 2. Among all women, the annual incidence of breast cancer was 1.7%, with similar estimates in women with (1.9%) and without an oophorectomy (1.6%). Among women with either a BRCA1 or BRCA2 mutation, oophorectomy was not associated with the risk of breast cancer compared with women who did not undergo an oophorectomy (Table 3). The age-adjusted hazard ratio was 0.91 (95% CI = 0.71 to 1.16, $P = .43$), and the multivariable hazard ratio was 0.89 (95% CI = 0.69 to 1.14, $P = .35$).

We stratified the cohort by BRCA mutation status. The annual incidence of breast cancer was 1.7% for BRCA1 and 1.5% for BRCA2 mutation carriers (Table 2). The age-adjusted hazard ratio associated with oophorectomy was 0.96 (95% CI = 0.73 to 1.26, $P = .76$) for BRCA1 and was 0.65 (95% CI = 0.37 to 1.16, $P = .14$) for BRCA2 mutation carriers (Table 4). After stratifying by age at diagnosis, oophorectomy was not associated with the risk of breast cancer prior to age 50 years among women with a BRCA1 mutation (HR = 0.79, 95% CI = 0.55 to 1.13, $P = .51$) (Table 4). In contrast, oophorectomy was associated with a statistically significant 82% reduction in breast cancer diagnosed prior to age 50 years among women with a BRCA2 mutation (HR = 0.18, 95% CI = 0.05 to 0.63, $P = .007$) but did not protect against breast cancer diagnosed after age 50 years (HR = 1.20, 95% CI = 0.51 to 2.83, $P = .70$). However, this was based on only three cases in the oophorectomy group with an annual risk of 0.5% (Table 2). We had information on estrogen receptor (ER) status for 41 of the 57 BRCA2 cases. The protective effect of oophorectomy on breast cancer diagnosed prior to age 50 years among ER-positive cases was very strong (HR = 0.10, 95% CI = 0.01 to 0.82, $P = .03$) (data not shown). There was not enough data to evaluate the relationship for ER-negative cases.

In a secondary analysis, we excluded women who had an oophorectomy prior to baseline (n = 857). This did not substantially alter the findings overall (HR = 1.14, 95% CI = 0.83 to 1.57, $P = .42$). The risk estimates were 1.26 (95% CI = 0.88 to 1.76, $P = .21$) for BRCA1 and 0.79 (95% CI = 0.34 to 1.81, $P = .57$) for BRCA2 mutation carriers (data not shown).

Discussion

The current study is the largest prospective analysis conducted to date of bilateral oophorectomy and breast cancer risk among women with an inherited BRCA1 or BRCA2 mutation. Among 3722 eligible participants, we identified 350 incident cancers. After a mean follow-up of 5.6 years, we found no statistically significant overall association between oophorectomy and breast cancer risk. We observed a statistically significant protective effect of oophorectomy on breast cancer risk prior to age 50 years among women with a BRCA2 mutation; however, this calculation was based on only three cases in the oophorectomy group. Although this finding was based on a post hoc analysis, the large sample size and long follow-up of our study, as well as the observation that risk reduction was in BRCA2 mutation carriers with predominantly ER-positive tumors, make it plausible.

There have been four prior prospective evaluations of oophorectomy and breast cancer risk in BRCA mutation carriers (1,5,9,10). In the most recent, which included 822 unaffected BRCA mutation carriers, 89 incident breast cancers, and a mean follow-up of 6.8 years in the oophorectomy group and 3.1 years in the no-oophorectomy group, Heemskerk-Gerristen et al. found no effect of oophorectomy on breast cancer risk (HR = 1.09, 95% CI = 0.67 to 1.77) (1). Similar to our findings, the risk estimates for oophorectomy and breast cancer risk differed for BRCA1 (HR = 1.21, 95% CI = 0.72 to 2.06) and BRCA2 (HR = 0.54, 95% CI = 0.17 to 1.66) mutation carriers, although the number of incident BRCA2 cancers was small (n = 14).

Among 988 unaffected BRCA mutation carriers enrolled in the EMBRACE study from the United Kingdom (64 incident breast cancers and follow-up of 3.4 years), Mavaddat et al., reported a borderline statistically significant protective effect of oophorectomy on breast cancer risk overall (HR = 0.62, 95% CI = 0.35 to 1.09) (10). For women with a BRCA1 mutation, the hazard ratio was 0.52 (95% CI = 0.24 to 1.13) and for BRCA2 mutation carriers the hazard ratio was 0.79 (95% CI = 0.35 to 1.80). There was a statistically significant reduction in risk if oophorectomy was performed prior to age 45 years (HR = 0.39, 95% CI = 0.17 to 0.87) but not after age 45 years (HR = 1.14, 95% CI = 0.50 to 2.61). The level of risk reduction was similar in carriers of either mutation. The major strength of this study was the inclusion of oophorectomy as a time-dependent variable; however, it was limited by the small number of incident cancers (35 BRCA1 cases and 29 BRCA2 cases) and short follow-up duration (3.4 years on average).

In a multicenter prospective analysis of 1370 BRCA mutation carriers enrolled in the PROSE study (262 incident cancers and 4.7 years of follow-up), Domcheck et al. reported a statistically significant protective effect of salpingo-oophorectomy on breast cancer risk overall (HR = 0.54, 95% CI = 0.37 to 0.79) with a hazard ratio of 0.63 (95% CI = 0.41 to 0.96) for BRCA1 and 0.36 (95% CI = 0.16 to 0.82) for BRCA2 mutation carriers (5). The risk-reducing effect was greater if oophorectomy was performed prior to age 50 years (HR = 0.51, 95% CI = 0.32 to 0.82). There was no

Table 1. Characteristics of *BRCA* mutation carriers with or without a bilateral oophorectomy

Variable	No oophorectomy (n = 2170)	Oophorectomy (n = 1552)	P*
Year of birth, mean (range)	1971.3 (1911–1993)	1957.5 (1908–1982)	<.001
Mean age at oophorectomy† (range), y	N/A	46.3 (13–78)	N/A
Age at baseline			
<30 y, No. (%)	935 (43.1)	30 (1.9)	
30–39 y, No. (%)	738 (34.0)	359 (23.1)	
40–49 y, No. (%)	297 (13.7)	644 (41.5)	
≥50 y, No. (%)	200 (9.2)	519 (33.4)	
Mean age (range), y	33.4 (13–85)	46.2 (21–88)	<.001
Mean follow-up (range), y	5.45 (0–21.18)	6.35 (0–19.50)	<.001
Breast cancer			
No, No. (%)	1963 (90.5)	1409 (90.8)	
Yes, No. (%)	207 (9.5)	143 (9.2)	.73
Mean age at diagnosis (range), y	42.5 (25–75)	52.5 (33–81)	<.001
BRCA mutation			
BRCA1‡, No. (%)	1782 (82.8)	1187 (77.0.0)	
BRCA2‡, No. (%)	370 (17.2)	355 (23.0)	
BRCA1 and *BRCA2* or missing, No.	18	10	<.001
Parity			
Nulliparous, No. (%)	908 (42.2)	189 (12.2)	
1 child, No. (%)	440 (20.5)	217 (14.1)	
2 children, No. (%)	486 (22.6)	652 (42.2)	
3 children, No. (%)	215 (10.0)	347 (22.5)	
≥4 children, No. (%)	102 (4.7)	139 (9.0)	
Mean No. children (range)	1.2 (0–10)	2.1 (0–8)	<.001
Missing, No.	19	8	<.001
Breastfeeding			
Never, No. (%)	1065 (51.7)	387 (28.7)	
Ever, <12 mo, No. (%)	562 (27.3)	539 (40.0)	
Ever, ≥12 mo, No. (%)	434 (21.1)	421 (31.3)	
Mean time breastfeeding (range), mo	6.9 (0–101)	10.3 (0–14)	<.001
Missing, No.	109	205	<.001
Oral contraceptive use at baseline			
Never, No. (%)	852 (39.4)	506 (32.9)	
Ever, No. (%)	1308 (60.6)	1031 (67.1)	
Missing, No.	10	15	<.001
Family history of breast cancer§			
0, No. (%)	809 (44.1)	562 (45.9)	
1, No. (%)	898 (49.0)	475 (38.8)	
2, No. (%)	98 (5.3)	157 (12.8)	
≥3, No. (%)	29 (1.6)	30 (2.5)	<.001
Mean No. family members with breast cancer (range)	0.6 (0–4)	0.7 (0–4)	
Missing, No.	336	328	.004
Age at menarche			
≤11 y, No. (%)	225 (10.7)	198 (13.2)	
12 y, No. (%)	485 (23.1)	357 (23.8)	
13 y, No. (%)	615 (29.3)	404 (26.9)	
≥14 y, No. (%)	774 (36.9)	542 (36.1)	
Mean age (range)	13.1 (9–19)	13.1 (9–28)	.09
Missing, No.	71	51	.47
Country of residence, No. (%)			
Poland	1158 (53.4)	448 (28.9)	
Canada	430 (19.80)	488 (31.4)	
Other	226 (10.4)	279 (18.0)	
United States	356 (16.4)	337 (21.7)	<.001

*P values were calculated using the Student's *t* test for continuous variables and the chi-square test for categorical variables. All tests were two-sided.
†Oophorectomy refers to bilateral oophorectomy.
‡Women with both a *BRCA1* and *BRCA2* mutation were coded as missing.
§Number of affected first-degree relatives.

effect of oophorectomy after age 50 years (HR = 1.36, 95% CI = 0.26 to 7.05). The annual incidence of breast cancer in the PROSE study was substantially higher than ours (4.4% vs 1.7%), and this suggests that a proportion of the breast cancer patients were ascertained for their study following their diagnosis (and unlikely to have had an oophorectomy prior to breast cancer).

In the earliest prospective publication, including 597 BRCA mutation carriers, 47 incident cancers, and three years of

follow-up, Kauff et al. reported a statistically significant 47% reduction in risk overall (95% CI = 0.29 to 0.96) that was stronger for BRCA2 (HR = 0.28, 95% CI = 0.08 to 0.92) than for BRCA1 (HR = 0.61, 95% CI = 0.30 to 1.22) mutation carriers, although both estimates were below unity (9). This study included women with a past history of breast cancer and did not use a time-dependent analysis.

Table 2. Person-years, number of incident breast cancers, and incidence of breast cancer among all women and stratified by oophorectomy status and *BRCA* mutation status

Variable	Person-years	No. of events	Incidence, %
BRCA1 and *BRCA2* mutation carriers (n = 3722)			
All	20 700	350	1.69
No oophorectomy*	13 052	207	1.59
Oophorectomy*	7648	143	1.87
BRCA1† mutation carriers (n = 2969)			
All	16 860	292	1.73
No oophorectomy*	10 806	170	1.57
Oophorectomy*	6055	122	2.02
BRCA2† mutation carriers (n = 725)			
All	3713	57	1.54
No oophorectomy*	1550	36	2.32
Oophorectomy*	2163	21	0.97
Censored at age 50 y‡			
BRCA1† mutation carriers (n = 2453)			
All	12 302	194	1.58
No oophorectomy*	9594	140	1.46
Oophorectomy*	2708	54	1.99
BRCA2† mutation carriers (n = 508)			
All	2156	30	1.39
No oophorectomy*	1585	27	1.70
Oophorectomy*	571	3	0.53

*Oophorectomy refers to bilateral oophorectomies only.
†Women with both a *BRCA1* and *BRCA2* mutation were coded as missing.
‡Follow-up was censored at age 50 years; thus, women older than age 50 years at baseline were excluded from this analysis.

These earlier publications were limited by small sample sizes, relatively short follow-up, and, in some cases, the inclusion of prevalent cases diagnosed prior to the date of ascertainment. In the current study, we included a large number of unaffected BRCA mutation carriers (n = 3720) who were followed from the date of ascertainment (ie, genetic testing or date of baseline questionnaire) and we treated oophorectomy as a time-dependent exposure (11). The relatively long follow-up period (5.6 years) allowed us to assess short- and long-term effects of oophorectomy. We had 350 incident cancers, the largest number for any study conducted to date.

Pathologic and etiologic differences between BRCA1- and BRCA2-associated breast cancers may help explain the differing effects of oophorectomy on risk (12). Tumors from women with a germline BRCA1 mutation are typically estrogen receptor (ER)–negative and progesterone receptor (PR)–negative, while those from women with a BRCA2 mutation are usually ER-positive and PR-positive and likely more responsive to stimulation by sex hormones (12). We had information on hormone receptor status for 77% of the breast cancer cases. In our study, women with a BRCA2 mutation were more likely to develop an ER-positive (80%) cancer compared with BRCA1 mutation carriers (27%). Among BRCA2 mutation carriers, we found a strong protective effect of oophorectomy for premenopausal/ER-positive breast cancers. It is biologically plausible that surgical removal of the endogenous source of sex hormones would differentially impact risk; however, these observations should be interpreted with caution given the small number of cases. It is perhaps surprising that oophorectomy does not influence BRCA1-associated breast cancer given that we and others have demonstrated a stronger role of reproductive factors and exogenous hormone exposure in BRCA1 but not BRCA2 mutation carriers (13–15). Furthermore, we recently showed that one to three years of tamoxifen protects against contralateral breast cancer

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Table 3. Bilateral oophorectomy and risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers

Variable	Age-adjusted HR (95% CI)	*P*	Multivariable* HR (95% CI)	*P*
Oophorectomy†				
No	1.00 (Referent)		1.00 (Referent)	
Yes	0.91 (0.71 to 1.16)	.43	0.89 (0.69 to 1.14)	.35
Family history of breast cancer‡				
0 family members	1.00 (Referent)		1.00 (Referent)	
1 family member	1.38 (1.06 to 1.76)	.01	1.36 (1.06 to 1.75)	.02
≥2 family members	1.34 (0.93 to 1.94)	.12	1.38 (0.95 to 2.00)	.09
Oral contraceptive use				
Never	1.00 (Referent)		1.00 (Referent)	
Ever	1.08 (0.87 to 1.35)	.48	1.38 (0.95 to 2.00)	.16
BRCA mutation				
BRCA1§	1.00 (Referent)		1.00 (Referent)	
BRCA2§	0.81 (0.62 to 1.08)	.15	0.86 (0.62 to 1.20)	.38
Country of residence				
Poland	1.00 (Referent)		1.00 (Referent)	
Canada	0.78 (0.59 to 1.03)	.08	0.77 (0.54 to 1.08)	.13
Other	1.00 (0.73 to 1.36)	.98	0.80 (0.48 to 1.34)	.41
United States	0.99 (0.74 to 1.34)	.96	0.97 (0.69 to 1.38)	.88

*Adjusted for the other variables in the model and also for age at menarche (≤12, 13, ≥14 years), parity (0, 1, 2, 3, ≥4 children), and breastfeeding (ever/never). CI = confidence interval; HR = hazard ratio.
†Oophorectomy was coded as a time-dependent covariate. Oophorectomy refers to bilateral oophorectomies only. Others variables were dichotomized based on exposure at baseline.
‡Number of affected first-degree relatives.
§Women with both a *BRCA1* and *BRCA2* mutation were coded as missing.

Table 4. Bilateral oophorectomy and risk of breast cancer, stratified by *BRCA* mutation status and by age at diagnosis

Variable	Age-adjusted HR (95% CI)	*P*	Multivariable* **HR (95% CI)**	*P*
All women				
BRCA1† mutation carriers				
Oophorectomy‡				
No	1.00 (Referent)		1.00 (Referent)	
Yes	0.96 (0.73 to 1.26)	.76	0.97 (0.73 to 1.29)	.85
BRCA2† mutation carriers				
Oophorectomy‡				
No	1.00 (Referent)		1.00 (Referent)	
Yes	0.65 (0.37 to 1.16)	.14	0.68 (0.38 to 1.21)	.19
Breast cancer diagnosed prior to age 50 y§				
BRCA1† mutation carriers				
Oophorectomy‡				
No	1.00 (Referent)		1.00 (Referent)	
Yes	0.79 (0.55 to 1.13)	.51	0.84 (0.58 to 1.21)	.34
BRCA2† mutation carriers				
Oophorectomy‡				
No	1.00 (Referent)		1.00 (Referent)	
Yes	0.18 (0.05 to 0.63)	.007	0.17 (0.05 to 0.61)	.006

*Adjusted for age at baseline (continuous), family history of breast cancer (0, 1, 2, ≥3 affected first-degree relatives), country of residence (Poland, Canada, United States, other) oral contraceptive use (ever/never), age at menarche (≤12, 13, ≥14 years), parity (0, 1, 2, 3, ≥4 children), and breastfeeding (ever/never). CI = confidence interval; HR = hazard ratio.

†Women with both a *BRCA1* and *BRCA2* mutation were coded as missing.

‡Oophorectomy was coded as a time-dependent covariate. Oophorectomy refers to bilateral oophorectomies only. Others variables were dichotomized based on exposure at baseline.

§Follow-up was censored at age 50 years; thus, women older than age 50 years at baseline were excluded from this analysis.

in women with a BRCA1 mutation (16), although the same protective effect of tamoxifen has also been shown for women with a BRCA2 mutation (17,18). In contrast, we recently showed no adverse effect of HRT use on risk after natural or surgical menopause among women with a BRCA1 mutation (19).

Among women in the general population, surgical menopause is associated with a reduction in breast cancer risk, likely through a reduction in the lifetime exposure to circulating ovarian hormones (20–22). The data also indicates a role of surgical ablation (surgical oophorectomy or ovarian irradiation) in the treatment of breast cancer among premenopausal women with ER-positive disease (23). However, surgical menopause (particularly at a young age and if without HRT) is not without its consequences. Data from observational studies and randomized controlled trials in the general population have shown that oophorectomy has a clinically significant adverse effect on mortality and other outcomes (24,25). In contrast, Finch and colleagues recently showed that oophorectomy was associated with a highly statistically significant 77% reduction in all-cause mortality in women with a BRCA1 or BRCA2 mutation (26). Of importance for BRCA mutation carriers with a prior breast cancer diagnosis is that oophorectomy is associated with a statistically significant reduction in the risk of contralateral breast cancer (RR = 0.53, 95% CI = 0.34 to 0.84), as well as a statistically significant reduction in breast cancer mortality (HR = 0.46, 95% CI = 0.27 to 0.79) (6,7). In addition, we have recently shown that a short course of HRT does not increase the risk of breast cancer among BRCA1 mutation carriers (19). Whether this is also true for women with a BRCA2 mutation is not yet known. There is clearly a need to balance the benefits and harms of surgical menopause in this population with substantially elevated lifetime risks of both breast and ovarian cancer.

Our study was not without limitations. This analysis included a small number of BRCA2 mutation carriers, particularly in the stratified analysis, and a relatively short follow-up period. In addition, information on hormone receptor status was missing for approximately 30% of the BRCA2 breast cancer cases.

In summary, ours is the largest prospective study to date evaluating the magnitude of protection associated with oophorectomy among BRCA mutation carriers. Our findings have important clinical implications. BRCA mutation carriers face high lifetime risks of developing breast, ovarian, and contralateral breast cancer (10). Although we failed to show an effect of oophorectomy on breast cancer overall, bilateral salpingo-oophorectomy should be recommended at age 35 years for BRCA1 mutation carriers and at age 40 years for BRCA2 mutation carriers. This is based on the ages at which the annual rates for ovarian cancer start to rise (26). The protective role of oophorectomy diagnosed prior to age 50 years further supports recommendations at age 40 years for BRCA2 mutation carriers. Additional studies with longer follow-up are warranted.

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