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EPIDEMIOLOGY

Oophorectomy and risk of contralateral breast cancer among *BRCA1* and *BRCA2* mutation carriers

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Abstract

Purpose Following a diagnosis of breast cancer, *BRCA* mutation carriers face an increased risk of developing a second (contralateral) cancer in the unaffected breast. It is important to identify predictors of contralateral cancer in order to make informed decisions about bilateral mastectomy. The impact of bilateral salpingo-oophorectomy (i.e., oophorectomy) on the risk of developing contralateral breast cancer is unclear. Thus, we conducted a prospective study of the relationship between oophorectomy and the risk of contralateral breast cancer in 1781 *BRCA1* and 503 *BRCA2* mutation carriers with breast cancer.

Methods Women were followed from the date of diagnosis of their first breast cancer until the date of diagnosis of a contralateral breast cancer, bilateral mastectomy, date of death, or date of last follow-up. Cox proportional hazards regression was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of contralateral breast cancer associated with oophorectomy. Oophorectomy was included as a time-dependent covariate. We performed a left-censored analysis for those women who reported a primary breast cancer prior to study entry (i.e., from completion of baseline questionnaire).

Results After an average of 9.8 years of follow-up, there were 179 (7.8%) contralateral breast cancers diagnosed. Oophorectomy was not associated with the risk of developing a second breast cancer (HR 0.92; 95% CI 0.68–1.25). The relationship did not vary by *BRCA* mutation type or by age at diagnosis of the first breast cancer. There was some evidence for a decreased risk of contralateral breast cancer among women with an ER-positive primary breast cancer, but this was based on a small number of events ($n = 240$).

Conclusion Overall, our findings suggest that oophorectomy has little impact on the risk of contralateral breast cancer.

Keywords *BRCA1/2* · Oophorectomy · Contralateral breast cancer

Introduction

There is conflicting evidence about the impact of bilateral salpingo-oophorectomy (referred to as oophorectomy hereafter) on the risk of breast cancer in *BRCA* mutation carriers. In early studies, oophorectomy was associated with a substantial reduction in the risk of a primary breast cancer; however, recent prospective reports show no such association [1, 2]. Nevertheless, oophorectomy prevents death from cancer [3, 4] and may prevent a second (contralateral) breast cancer [5, 6]. These seemingly contradictory findings may represent true associations or may be spurious due to methodologic differences and biases.

We conducted a prospective study of the association between oophorectomy and the risk of contralateral breast cancer among women with a *BRCA1* or *BRCA2* mutation. We evaluated whether the association differed for various subgroups, including by age at diagnosis and by estrogen receptor status of the first cancer. It is important to have an accurate knowledge of the risk of contralateral breast cancer as well as the predictors of contralateral cancer in order to make informed decisions about bilateral mastectomy.

The other members of the Hereditary Breast Cancer Clinical Study Group are listed in the Acknowledgments.

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Materials and methods

Study population

Eligible study subjects included female *BRCA1* and *BRCA2* mutation carriers from 80 participating centers in 17 countries who were enrolled in a multicenter, longitudinal study. All subjects had sought testing for *BRCA1* and *BRCA2* mutations because of a personal or family history of breast and/or ovarian cancer. Mutation detection was performed using a range of techniques, but all nucleotide sequences were confirmed by direct sequencing of DNA. All study subjects (with the exception of some from the University of Utah and University of California Irvine) received genetic counseling. The study was approved by the institutional ethics review boards of the host institutions and all study subjects provided written informed consent.

Data collection

All subjects completed a baseline research questionnaire at the time of a clinic appointment or at their home at a later date. The questionnaires requested detailed information on family and personal history of cancer, reproductive and medical histories (including preventive surgery), as well as medication use. Follow-up questionnaires are completed every two years thereafter to update exposure information and to capture incident disease. Questionnaires are either mailed to each participant to complete and return, or administered over the phone by a genetic counselor or research assistant. Information on diagnoses and treatment of breast cancer (including date of diagnosis, chemotherapy, surgery) was collected from the questionnaires. Hormone receptor status of the tumor and other pathologic features were abstracted from pathology report and/or medical record review.

Subjects available for analysis

For the current analysis, we only included women who were diagnosed with a unilateral breast cancer at study enrolment or during the follow-up period. There were 16,400 *BRCA1* and *BRCA2* mutation carriers identified for this analysis. Subjects were not eligible for inclusion if they did not report a diagnosis of unilateral breast cancer at study enrolment ($n = 9770$), had a previous diagnosis of cancer (other than unilateral breast cancer) including bilateral breast cancer ($n = 1958$), did not complete at least one follow-up questionnaire or were lost to follow-up ($n = 1827$), had a bilateral mastectomy for the treatment of their primary breast cancer ($n = 50$), a unilateral mastectomy in the unaffected breast ($n = 594$) or had missing key information including detail surrounding the diagnosis and treatment of their primary cancer (i.e., date of breast cancer, date of oophorectomy)($n = 291$). After these exclusions, there was a total of 1910 women who reported a unilateral, first primary invasive breast cancer at the time of enrollment (baseline questionnaire).

In the identification of the cohort with both an incident primary and contralateral breast cancer, we excluded who were not diagnosed with breast cancer in the follow-up period ($n = 4348$), were diagnosed with breast cancer at baseline ($n = 6719$), or with any other cancer at baseline (2325). We also excluded women who were lost to follow-up or did not complete at least one follow-up questionnaire ($n = 2489$), had a prophylactic mastectomy prior to their primary breast cancer diagnosis ($n = 98$), or were missing other relevant information ($n = 28$). There was a total of 393 women with a diagnosis of an incident primary and contralateral breast cancer.

Statistical analysis

Women were followed from the date of diagnosis of their first breast cancer until either the date of diagnosis of a contralateral breast cancer, bilateral mastectomy, date of death, or date of completion of their last follow-up questionnaire. We performed a left-censored analysis for those women who reported primary breast cancer at study entry (i.e., they were followed from the date of completion of their baseline questionnaire).

The Cox proportional hazards model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of contralateral breast cancer associated with oophorectomy. Oophorectomy was included as a time-dependent covariate. 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. In the multivariate analysis, we adjusted for and age at diagnosis (≤ 40, 41–50, > 50 years), *BRCA* mutation (*BRCA1* vs. *BRCA2*), tamoxifen (no, yes), chemotherapy (no, yes), radiation (no, yes), and surgery for the primary breast cancer (no surgery, lumpectomy, unilateral mastectomy). We also conducted analyses stratified by age at diagnosis of the primary breast cancer, by *BRCA* mutation type, and by estrogen receptor status of the initial breast cancer. Subjects who carried both a *BRCA1* and *BRCA2* mutation were categorized as *BRCA1* mutation carriers ($n = 19$).

All analyses were conducted using the SAS statistical package, version 9.4 software (SAS Institute, Cary, NC, USA). All P values were two-sided and were considered statistically significant if $P \leq 0.05$.

Results

There were 2303 *BRCA1* and *BRCA2* mutation carriers with breast cancer included in the analysis. Of these, 1910 (83%) were diagnosed prior to enrollment into the study (i.e., diagnosed before the baseline questionnaire) and 393 (17%) were incident cancers (i.e., diagnosed after the baseline questionnaire). The characteristics of these women are displayed in Table 1. There were 179 (7.8%) contralateral breast cancers diagnosed in the follow-up period between the date of questionnaire completion (i.e., study entry) and the end of follow-up (mean follow-up = 9.8 years). The average age of diagnosis of the first breast cancer was 44.4 years (range 19–82) and the average age of diagnosis of the contralateral breast cancer was 52.6 years (range 27–78).

A total of 1515 (66%) of the women included in this analysis underwent a bilateral oophorectomy at some time and 788 did not (34%). Of the women with an oophorectomy, 327 (22%) had the surgery prior to the first breast cancer, 250 (17%) underwent surgery within one year of their diagnosis, and 938 (62%) underwent surgery one or more years following their diagnosis. The overall 10-year and 20-year cumulative rates of contralateral breast cancer were 13% and 26%, respectively. Among *BRCA1* mutation carriers, the 10-year cumulative rate was 15% and the 20-year cumulative rate was 28%. For *BRCA2* mutation carriers, the corresponding rates were 6% and 16%.

Among all women combined, there was no significant association between oophorectomy and the risk of contralateral breast cancer (Table 2). The multivariate association with oophorectomy was HR was 0.92 (95% CI 0.68–1.25). The HR was 0.98 (95% CI 0.71–1.30) for *BRCA1* mutation carriers and was 0.75 (95% CI 0.30–189) for *BRCA2* mutation carriers. Among women who were diagnosed at or before age 50, the HR was 0.88 (95% CI 0.64–1.23). Among women diagnosed after age 50, the HR was 1.10 (95% CI 0.52–2.34) (Table 2).

Information on ER status was available for only 633 of the women (27%) (Table 3). Among 393 women with initial breast cancer that was ER-negative, there was no significant relationship between oophorectomy and the risk of contralateral breast cancer ($HR_{multivariate}$ 1.02; 95% CI 0.56–187). In contrast, among the 240 women diagnosed with an ER-positive primary tumor, oophorectomy was associated with a large reduction in the risk of contralateral breast cancer ($HR_{multivariate}$ 0.22; 95% CI 0.07–0.68); however, this estimate was based on only 19 incident cases.

The risk estimates were not significantly influenced by the timing of oophorectomy (i.e., prior to vs. following the first diagnosis of breast cancer) (data not shown).

Discussion

In this prospective analysis of 2303 women with a first diagnosis of unilateral breast cancer, we observed no overall impact of oophorectomy on the risk of contralateral breast cancer (HR 0.92; 95% CI 0.68–1.25). However, we did observe a significant 78% reduction in the risk among women who were initially diagnosed with an ER-positive tumor (HR 0.22; 95% CI 0.07–0.68). This risk reduction was limited to women with a primary cancer diagnosed prior to age 50 (HR 0.12; 95% CI 0.03–0.47). These findings should be interpreted with caution since hormone receptor status was only available for a minority of the women (27%) and the number of events was small.

The evidence presented here is strong but not conclusive. This relationship is not consistent in all subgroups and is dependent on several factors including hormone receptor status of the initial breast cancer, and age at diagnosis. In an earlier study, Metcalfe and colleagues evaluated the impact of treatment factors on the risk of contralateral breast cancer among 810 *BRCA* mutation carriers with stage I or II breast cancer [5]. Oophorectomy was associated with a 47% reduction in the risk of contralateral breast cancer ($HR_{overall}$ 0.53; 95% CI 0.34–0.84). Estimates were similar for *BRCA1* (HR 0.48; 95% CI 0.27–0.84) and *BRCA2* (HR 0.49; 95% CI 0.21–1.17) mutation carriers. Furthermore, this protective effect was significant for women diagnosed before age 50 (HR 0.39; 95% CI 0.23–0.67), but not after age 50 (HR 0.90; 95% CI 0.30–2.64). Metcalfe et al., did not stratify by ER status of the initial breast cancer diagnosis. In contrast, we did not see a protective effect of oophorectomy in our analysis among all women with a primary breast cancer diagnosed prior to age 50.

In an analysis of 651 *BRCA* mutation carriers with unilateral breast cancer, Mavaddat et al. observed a borderline significant reduction in the risk of contralateral breast cancer among all carriers combined ($HR_{overall}$ 0.59; 95% CI 0.35–0.99), particularly with oophorectomy prior to age 45 ($HR_{overall}$ 0.51; 95% CI 0.26–0.99). In their stratified analysis, the significant reduction in the risk of contralateral breast cancer with oophorectomy was limited to *BRCA2* ($n = 309$; HR 0.16; 95% CI 0.04–0.66) but not *BRCA1* ($n = 340$; HR 0.77; 95% CI 0.41–1.45) mutation carriers [6]. Although they did not report on risk estimates by ER status, these findings support a role for oophorectomy in preventing ER-positive disease given that *BRCA2* mutation carriers tend to develop hormone receptor-positive tumors [7]. They did not stratify by age at diagnosis of the initial cancer. In contrast, two other studies have reported no association between oophorectomy and a second breast cancer [3, 8].

In 2017, we reported no impact of oophorectomy on the risk of a first primary breast cancer ($HR_{overall}$ 0.89; 95%

Table 1 Characteristics of *BRCA1* and *BRCA2* mutation carriers with a diagnosis of breast cancer

Variables	Prevalent primary breast cancer ($n=1910$)[a]	Incident primary breast cancer ($n=393$)[b]	Prevalent and incident combined ($n=2303$)
Year of birth, mean (range)	1955.3 (1913–1990)	1961.9 (1929–1987)	1956.5 (1913–1990)
Age at baseline, mean (range)	49.4 (24–91)	42.0 (18–76)	48.1 (18–91)
Mean follow-up, years (range)			
Primary diagnosis to baseline	5.4 (0–42)		
Baseline to primary diagnosis		4.5 (0–17.6)	
Baseline to end of follow-up	5.8 (0–26)		
Primary diagnosis to end of follow-up	11.2 (0.1–59)	3.0 (0.0–18)	9.8 (0–59)
Age at primary diagnosis, *n* (%)			
≤ 40	734 (38.4%)	121 (30.8%)	855 (37.1%)
41–50	739 (38.7%)	128 (32.6%)	867 (37.7%)
> 50	437 (22.9%)	144 (36.6%)	581 (25.2%)
Mean age at diagnosis, years (range)	43.9 (19–82)	46.6 (25–81)	44.4 (19–82)
Contralateral breast cancer, *n* (%)			
No	1737 (90.9%)	387 (98.5%)	2124 (92.2%)
Yes	173 (9.1%)	6 (1.5%)	179 (7.8%)
Mean age at diagnosis	52.8 (27–78)	46.8 (38–56)	52.6 (27–78)
BRCA mutation, *n* (%)			
BRCA1	1462 (76.5%)	319 (81.2%)	1781 (77.3%)
BRCA2	430 (22.5%)	73 (18.6%)	503 (21.8%)
BRCA1 and *BRCA2* or missing	18 (0.9%)	1 (0.3%)	19 (0.8%)
Tamoxifen, *n* (%)			
No	1261 (66.0%)	211 (53.7%)	1472 (63.9%)
Yes	621 (32.5%)	89 (22.7%)	710 (30.8%)
Missing	28 (1.5%)	93 (23.7%)	121 (5.2%)
Chemotherapy, *n* (%)			
No	360 (18.9%)	86 (21.9%)	446 (19.4%)
Yes	1529 (80.1%)	258 (65.7%)	1787 (77.6%)
Missing	21 (1.1%)	49 (12.5%)	70 (3.0%)
Radiation therapy, *n* (%)			
No	799 (41.8%)	220 (56.0%)	1019 (44.3%)
Yes	1076 (56.7%)	113 (28.8%)	1189 (51.6%)
Missing	35 (1.8%)	60 (15.3%)	95 (4.1%)
Surgery, *n* (%)			
Unilateral mastectomy	1020 (53.4%)	253 (64.4%)	1273 (55.3%)
No surgery	48 (2.5%)	31 (7.9%)	79 (3.4%)
Lumpectomy[c]	820 (44.2%)	95 (24.2%)	915 (39.7%)
Missing	22 (1.2%)	14 (3.6%)	36 (1.6%)
Oophorectomy, *n* (%)[d]			
No	665 (34.8%)	123 (31.3%)	788 (34.2%)
Yes	1245 (65.2%)	270 (68.7%)	1515 (65.8%)
Timing, *n* (%)			
Prior to first breast cancer diagnosis	173 (13.9%)	154 (57.0%)	327(21.6%)
At first breast cancer diagnosis	222 (17.8%)	28 (10.4%)	250 (16.5%)
After first breast cancer diagnosis	850 (68.3%)	88 (32.6%)	938 (61.9%)
ER status of primary breast cancer, *n* (%)			
Positive	126 (6.6%)	114 (29%)	240 (10.4%)
Negative	229 (12%)	164 (42%)	393 (17.1%)
Equivocal	12 (0.6%)	22 (5.6%)	34 (1.5%)
Unknown/blank	1543 (80.8%)	86 (21.9%)	1636 (71.0%)

Table 1 (continued)

[a]Includes women with a primary breast cancer at the time of the baseline questionnaire

[b]Includes women who developed an incident primary breast cancer (i.e., following the baseline questionnaire)

[c]Lumpectomy includes women who had a lumpectomy followed by a unilateral mastectomy

[d]Censored at prophylactic mastectomy or diagnosis of contralateral breast cancer

Table 2 Oophorectomy and risk of contralateral breast cancer among all women combined and by *BRCA* mutation type or age at diagnosis of the first breast cancer

Oophorectomy[a]	Controls (%)/cases (%)	Univariate RR (95% CI)	*P*	Multivariate RR[b] (95% CI)	*P*
All women					
No	712 (34%)/76 (42%)	1.00 (reference)		1.00 (reference)	
Yes	1412 (66%)/103 (57%)	0.90 (0.67–1.21)	0.49	0.92 (0.68–1.25)	0.61
BRCA1 mutation carriers					
No	561 (35%)/65 (41%)	1.00 (reference)		1.00 (reference)	
Yes	1062 (65%)/93 (59%)	0.89 (0.65–1.23)	0.49	0.98 (0.71–1.36)	0.91
BRCA2 mutation carriers					
No	146 (30%)/10 (50%)	1.00 (reference)		1.00 (reference)	
Yes	377 (70%)/10 (50%)	0.86 (0.36–2.08)	0.74	0.75 (0.30–1.89)	0.12
Primary breast cancer ≤ 50					
No	553 (35%)/65 (44%)	1.00 (reference)		1.00 (reference)	0.62
Yes	1022 (65%)/82 (56%)	0.88 (0.64–1.22)	0.45	0.88 (0.64–1.23)	
Primary breast cancer > 50					
No	159 (29%)/11(34%)	1.00 (reference)		1.00 (reference)	
Yes	390 (71%)/21(66%)	1.03 (0.50–2.14)	0.94	1.10 (0.52–2.34)	0.79

[a]Oophorectomy treated as a time-dependent variable

[b]Multivariate analysis adjusted for *BRCA* mutation (*BRCA1* vs. *BRCA2*), tamoxifen (no, yes), chemotherapy (no, yes), radiation (no, yes), primary surgery (no surgery, lumpectomy, unilateral mastectomy), and age at diagnosis (≤40, 41–50, > 50) [except for the analysis stratified by age of primary breast cancer]

Table 3 Oophorectomy and risk of contralateral breast cancer by ER status of the first breast cancer, all women combined and by age at diagnosis of the first breast cancer

Oophorectomy[a]	Controls (%)/cases (%)	(95% CI)	*P*	Multivariate RR[b] (95% CI)	*P*
All women					
ER-negative					
No	111 (33%)/20 (37%)	1.00 (reference)		1.00 (reference)	
Yes	228 (67%)/34 (63%)	1.04(0.59–1.83)	0.9	1.02(0.56–1.87)	0.94
ER-positive					
No	48 (22%)/11 (58%)	1.00 (reference)		1.00 (reference)	
Yes	173 (78%)/8 (42%)	0.42(0.17–1.04)	0.06	0.22(0.07–0.68)	0.008[a]
				0.42(0.17–1.04)	0.06[b]
Primary breast cancer ≤ 50					
ER-negative					
No	90 (36%)/17 (38%)	1.00 (reference)		1.00 (reference)	
Yes	160 (64%)/28 (62%)	1.12(0.59–2.10)	0.74	1.00(0.51–1.94)	0.99
ER-positive					
No	32 (23%)/10 (59%)	1.00 (reference)		1.00 (reference)	
Yes	106 (77%)/7 (41%)	0.43 (0.17–1.15)	0.09	0.12(0.03–0.47)	0.003

[a]Oophorectomy treated as a time-dependent variable

[b]Multivariate analysis adjusted for *BRCA* mutation (*BRCA1* vs. *BRCA2*), tamoxifen (no, yes), chemotherapy (no, yes), radiation (no, yes), primary surgery (no surgery, lumpectomy, unilateral mastectomy), and age at diagnosis (≤40, 41–50, > 50) [except for the analysis stratified by age of primary breast cancer]

CI 0.69–1.14) but a reduction in the risk of *BRCA2*-cancer diagnosed under 50 (HR 0.17; 95% CI 0.05–0.61) [2]. In the current analysis, the protective effect of oophorectomy on the risk of contralateral breast cancer was apparent for women who had an initial diagnosis of an ER-positive cancer, in particular those diagnosed under age 50. Collectively, the findings suggest that the impact of ovarian hormonal withdrawal (due to oophorectomy) on both a first and contralateral breast cancer is likely limited to early-onset, hormone-responsive cancers.

There have been a few reports comparing the pathologic features of the primary and contralateral breast cancer of *BRCA* mutation carriers. In a study of 286 women with contralateral breast cancer, Weitzel et al., reported that ER status of the primary tumor was a significant predictor of the ER status of the second tumor (odds ratio = 9.7; 95% CI 3.5–21.5) [9]. This was true for *BRCA1* ($n = 211$) and *BRCA2* ($n = 75$) mutation carriers. Mavvaddat et al., similarly demonstrated strong concordance in ER status of a first invasive and the contralateral breast tumor in *BRCA* mutation carriers ($n = 1022$) [7].

Limitations of the current study included small sample sizes in various strata, missing information on hormone receptor status for a large proportion of the primary breast cancers (71%), and the inclusion of prevalent, primary breast cancers. However, all contralateral breast cancers were diagnosed after completion of the baseline questionnaire. Furthermore, we had detailed and updated exposure and covariate information on a large number of eligible *BRCA* mutation carriers, a relatively long follow-up period, and our analysis included oophorectomy as a time-dependent exposure. We performed a left-censored analysis to account for person-time between the date of diagnosis and study enrolment among the women who had a primary breast cancer before study entry.

In our current analysis, the 20-year cumulative risk of contralateral breast cancer was 28% for *BRCA1* mutation carriers and 16% for *BRCA2* mutation carriers. In a prospective study of 2213 *BRCA* mutation carriers, Kuchenbaecker et al., estimated the 20-year cumulative risk of contralateral breast cancer to be 40% for women with a *BRCA1* mutation and 26% for women with a *BRCA2* mutation [10]. In a recent report of 941 Polish *BRCA1* mutation carriers with a prior diagnosis of breast cancer, we reported a 20-year cumulative incidence of 31% (annual risk of 1.96%) for contralateral breast cancer (in press). These findings reiterate that the risk of developing a new invasive breast cancer on the contralateral side is substantially increased among *BRCA* mutation carriers with a prior diagnosis of breast cancer [11].

Despite the lack of a protective effect on developing a second breast cancer, oophorectomy is still advised for this high-risk population to prevent ovarian cancer and improving all-cause mortality [4]. Bilateral mastectomy is the most effective treatment at the time of a primary breast cancer in a women with a *BRCA1* or *BRCA2* mutation in terms of reducing the incidence of a second primary breast cancer and potentially improving survival. Future prospective studies that include women with both incident primary and contralateral breast cancer and detailed information on hormone receptor status are needed to clarify a role of oophorectomy.

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Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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