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ORIGINAL REPORT

Breast Cancer Risk Following Bilateral Oophorectomy in *BRCA1* and *BRCA2* Mutation Carriers: An International Case-Control Study

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ABSTRACT

Purpose
The purpose of this study was to estimate the extent of protection offered against breast cancer by prophylactic oophorectomy in carriers of *BRCA1* or *BRCA2* mutations and to determine to what extent risk reduction varies with age at oophorectomy, age at diagnosis, and time elapsed since surgery.

Patients and Methods
We analyzed 1,439 patients with breast cancer and 1,866 matched controls derived from a registry of *BRCA1* and *BRCA2* carriers. We estimated odds ratios (ORs) of breast cancer for having had a bilateral oophorectomy, using conditional logistic regression, matched for parity and for oral contraceptive use.

Results
A previous history of oophorectomy was associated with a significant reduction in breast cancer risk of 56% for *BRCA1* carriers (OR = 0.44; 95% CI, 0.29 to 0.66) and of 46% for *BRCA2* carriers (OR = 0.57; 95% CI, 0.28 to 1.15). The risk reduction was greater if the oophorectomy was performed before age 40 (OR = 0.36; 95% CI, 0.20 to 0.64 for *BRCA1* carriers) than after age 40 (OR = 0.53; 95% CI, 0.30 to 0.91). The protective effect was evident for 15 years post-oophorectomy (OR = 0.39; 95% CI, 0.26 to 0.57).

Conclusion
Oophorectomy is an effective means of reducing the risk of breast cancer in carriers of *BRCA1* mutations. The data suggest oophorectomy is protective in *BRCA2* carriers as well, but needs to be confirmed in other studies.

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INTRODUCTION

Women with a germline mutation in *BRCA1* or *BRCA2* face increased risks of breast and ovarian cancers. For *BRCA1* mutation carriers, the estimated lifetime risk of breast cancer ranges from 40% to 85%,[1-4] and the estimated lifetime risk of ovarian cancer ranges from 20% to 65%.[1-4] For *BRCA2* mutation carriers, the breast cancer risk is similar, but the lifetime risk of ovarian cancer is approximately 20%.[1-4] Strategies for risk reduction include preventive surgery and chemoprevention. Increased surveillance is recommended. Bilateral prophylactic oophorectomy is commonly recommended to *BRCA1* and *BRCA2* mutation carriers to reduce the risk of ovarian cancer and breast cancer. Approximately 60% of women with *BRCA1* or *BRCA2* mutations in Canada now undergo prophylactic oophorectomy within 1 year of having been demonstrated to carry a *BRCA* mutation (Metcalf et

al,[7] The use of tamoxifen and other preventive measures among healthy women who carry a *BRCA1* or *BRCA2* mutation, manuscript submitted for publication). Case-control studies in the general population have shown that bilateral oophorectomy in premenopausal women is associated with a significant reduction in breast cancer risk.[5,6] Several studies have also shown that oophorectomy is effective in reducing the risk of primary and contralateral breast cancer in *BRCA1* and *BRCA2* carriers.[7-10] However, previous studies have been small and there was not sufficient data to estimate the magnitude of risk reduction by age of oophorectomy or by *BRCA1*/*BRCA2* mutation status, or to measure the duration of the protective effect.

PATIENTS AND METHODS

Study Subjects

Women with a *BRCA1* or *BRCA2* mutation were identified through a registry of mutation carriers at the Centre for Research in Women's Health at the University of Toronto. Data were collected from women with known pathogenic *BRCA1* and *BRCA2* mutations at 48 different centers in seven countries in North America, Europe, and Israel. All patients provided informed written consent for genetic testing. The study has been approved by the ethics committees/human subjects review boards of all participating centers. In most cases, testing was offered initially to women who were affected either by breast cancer or ovarian cancer. When a mutation in either *BRCA1* or *BRCA2* was found in a proband or in her relative, testing was offered to other at-risk women in her family. Mutation detection was performed using a range of techniques, but all nucleotide alterations were confirmed by direct sequencing of DNA. A woman was eligible for the study when the molecular analysis established that she was a mutation carrier.

There were 5,659 mutation carriers in the database. Of these, 851 patients with ovarian cancer and 92 women with bilateral prophylactic mastectomy were excluded. An additional 147 patients were excluded because information was missing on key variables (ie, parity, oophorectomy, etc.). This left 4,569 subjects eligible for the study. There were 2,283 women with a mutation and breast cancer who were eligible to be patient cases. There were 2,286 women without breast cancer who were eligible to be patient controls. Patient cases and patient controls were matched by year of birth (within 1 year), country of residence, and *BRCA1* or *BRCA2* mutation status. The matched patient control was at risk for breast cancer at least until the age of diagnosis of the matched patient case. In total, 1,439 matched sets were identified. There was an average of 1.3 patient controls per patient case (range, one to nine). Thirteen patients had a mutation in both genes. These patients were excluded from subset analyses.

Study Protocol

At each center, patients completed a questionnaire regarding their personal history of cancer and potential cancer risk factors. These included questions about oophorectomy, mastectomy, reproductive and menopausal history, smoking, oral contraceptive use, and hormone replacement use. At some centers, the questionnaires were completed by telephone interview. Patients were asked if they had ever had an oophorectomy, if one or two ovaries were removed, and at what age the oophorectomy was performed. Only bilateral oophorectomies were considered as exposures. Oophorectomies could have been done for cancer prophylaxis or for other reasons. Only oophorectomies that took place before the diagnosis of breast cancer (ie, in different calendar years) in the patients were considered as exposures. Similarly, only oophorectomies that took place before the age of diagnosis of breast cancer in the matched patient case were considered to be exposures for the patient controls.

Study Design and Statistical Analysis

The frequency of oophorectomy was compared in *BRCA1* and *BRCA2* mutation carriers with and without a history of breast cancer using a matched case-control analysis with variable number of controls. The odds ratios (ORs) and *P* values for breast cancer associated with oophorectomy were calculated using conditional logistic regression, implemented in SAS (SAS Institute Inc, Cary, NC).

RESULTS

In total, 1,439 matched sets were identified (1,060 in *BRCA1* and 379 in *BRCA2*). The characteristics of the patient cases and patient controls are shown in Table 1. Approximately three quarters of the subjects were *BRCA1* mutation carriers. Patient cases and patient controls were similar for age,

Table 1. Characteristics of Patient Cases and Patient Controls

Variables	Patient Case (n = 1,439)	Patient Control (n = 1,866)
Age, years		
Mean	46.4	45.9
No.	1,953.4	1,954.1
Mutation, %		
BRCA1	73.6	73.6
BRCA2	26.4	26.4
Age of Dx, years		
BRCA1	38.9	N/A
BRCA2	40.9	
Parity		
Nulliparous, %	20.8	21.1
Mean	1.9	1.9
Oral contraceptives		
Ever used, %	68.8	69.8
Mean years used, SD	3.9	3.8
Ethnic ground		
Jewish		
No.	379	469
%	26.3	25.1
French Canadian		
No.	134	142
%	9.3	7.6
Other White		
No.	894	1,228
%	62.2	65.8
Other		
No.	32	27
%	2.2	1.5

Abbreviations: Dx, diagnosis; SD, standard deviation.

Table 2. Association Between Oophorectomy and Breast Cancer

Mutation	Unadjusted			Adjusted		
	OR	*P*	95% CI	OR	*P*	95% CI
BRCA1 or *BRCA2*	0.46	.00001	0.32 to 0.65	0.46	.00001	0.32 to 0.65
BRCA1	0.43	.00006	0.29 to 0.65	0.44	.00006	0.29 to 0.66
BRCA2	0.57	.11	0.28 to 1.15	0.57	.11	0.28 to 1.15

NOTE. Adjusted by oral contraceptive (yes/no) and parity (0, 1, 2, 3…). All ORs were calculated by conditional logistic regression.
Abbreviation: OR, odds ratio.

parity, and oral contraceptive use. The mean age of breast cancer diagnosis in patient cases was 38.9 years for *BRCA1* carriers and was 40.9 years for *BRCA2* carriers.

Fifty-one of the patient cases (3.5%) had an oophorectomy before breast cancer, versus 115 of the patient controls (6.2%). These proportions were similar for subgroups with *BRCA1* and *BRCA2* mutations. Oophorectomy was associated with a 57% reduction in breast cancer risk in *BRCA1* carriers (unadjusted OR = 0.43; $P = .00006$) and a 46% risk reduction in *BRCA2* carriers (OR = 0.57; $P = .11$). The observed reduction persisted after adjustment for oral contraceptive use and parity (Table 2).

The effect of age at oophorectomy on subsequent breast cancer risk was examined (Table 3). For *BRCA1* carriers, the OR was 0.36 for oophorectomies performed at age 40 or younger and was 0.50 for oophorectomies performed from age 40 to 50. There was a small risk reduction associated with oophorectomies performed after age 50 (OR = 0.66) but there were few subjects in this category, and the result was not statistically significant. Among *BRCA2* carriers there was no clear trend associated with age of oophorectomy, but this was a much smaller group and none of the subgroup estimates were statistically significant.

To determine if oophorectomy conferred protection against both early- and late-onset hereditary breast cancer, we examined the association between age at breast cancer diagnosis and prior oophorectomy (Table 4). When carriers of both *BRCA1* and *BRCA2* mutations were considered together, prior oophorectomy was associated with a greater reduction in the risk of breast cancer diagnosed at age 40 or younger (OR = 0.33; $P = .006$) or between ages 41 and 50 (OR = 0.43; $P = .001$) than for cases diagnosed above age 50 (OR = 0.64; $P = .14$).

Among patient cases, the average time interval between the ovarian surgery and the diagnosis of breast cancer was 7.2 years for *BRCA1* mutation carriers (range, 1 to 29 years) and was 10.5 years for *BRCA2* mutation carriers (range, 2 to 29 years). The protective effect of oophorectomy was evident for 15 years after surgery (Table 5). In carriers of *BRCA1* mutations, the OR for breast cancer within 15 years

Table 3. Association Between Age at Oophorectomy and Breast Cancer

Age at Oophorectomy, Years	No. With Oophorectomy		Unadjusted			Adjusted*		
	Patient Case	Patient Control	OR	*P*	95% CI	OR	*P*	95% CI
BRCA1/2								
No oophorectomy	1,388	1,751	1.0	—	—	1.0	—	—
≤ 40	23	59	0.41	.0004	0.25 to 0.68	0.41	.0005	0.25 to 0.68
41-50	21	47	0.47	.005	0.28 to 0.79	0.47	.005	0.28 to 0.80
51+	7	9	0.71	.53	0.25 to 2.06	0.70	.51	0.24 to 2.03
BRCA1								
No oophorectomy	1,021	1,320	1.0	—	—	1.0	—	—
≤ 40	17	50	0.36	.0004	0.20 to 0.63	0.36	.0005	0.20 to 0.64
41-50	16	34	0.49	.02	0.27 to 0.91	0.50	.02	0.27 to 0.92
51+	5	7	0.67	.50	0.21 to 2.13	0.66	.48	0.21 to 2.09
BRCA2								
No oophorectomy	360	426	1.0	—	—	1.0	—	—
≤ 40	6	9	0.70	.49	0.25 to 1.96	0.69	.49	0.25 to 1.95
41-50	5	12	0.43	.12	0.15 to 1.23	0.44	.12	0.15 to 1.24
51+	2	2	1.00	1.00	0.06 to 16.0	1.00	1.00	0.06 to 16.1

Abbreviation: OR, odds ratio.
*Adjusted by oral contraceptive (yes/no) and parity (0, 1, 2, 3,…). All ORs were calculated by conditional logistic regression.

Table 4. Association Between Age at Breast Cancer Diagnosis and Oophorectomy

Age at Breast Cancer Diagnosis, Years	Sets	No. with Oophorectomy		Unadjusted			Adjusted*		
		Patient Case	Patient Control	OR	*P*	95% CI	OR	*P*	95% CI
BRCA1/2									
≤ 40	862	8	28	0.33	.006	0.15 to 0.72	0.33	.006	0.15 to 0.73
41-50	451	22	56	0.43	.002	0.26 to 0.72	0.43	.001	0.25 to 0.72
51+	126	21	31	0.63	.14	0.34 to 1.16	0.64	.14	0.35 to 1.17
BRCA1									
≤ 40	668	6	27	0.26	.003	0.11 to 0.62	0.26	.003	0.11 to 0.64
41-50	306	16	42	0.42	.006	0.23 to 0.78	0.42	.006	0.23 to 0.79
51+	85	16	22	0.68	.29	0.34 to 1.39	0.68	.29	0.34 to 1.38
BRCA2									
≤ 40	189	2	1	2.00	.57	0.18 to 22.1	2.01	.57	0.18 to 22.4
41-50	143	6	14	0.46	.11	0.17 to 1.19	0.46	.10	0.18 to 1.22
51+	41	5	8	0.57	.37	0.17 to 1.95	1.02	.97	0.25 to 4.16

Abbreviation: OR, odds ratio.
*Adjusted by oral contraceptive (yes/no) and parity (0, 1, 2, 3,...). All ORs were calculated by conditional logistic regression.

of oophorectomy was 0.38 (95% CI, 0.25 to 0.59) and more than 15 years after oophorectomy was 1.27 (95% CI, 0.38 to 4.17). In carriers of *BRCA2* mutations, the OR for breast cancer within 15 years of oophorectomy was 0.43 (95% CI, 0.19 to 0.99) and more than 15 years of oophorectomy was 1.47 (95% CI, 0.32 to 6.64). When both groups were considered together, there was a highly significant reduction in breast cancer risk within 15 years of oophorectomy (OR 0.39; $P = .000003$), but no evidence of risk reduction thereafter (OR 1.32; 95% CI, 0.52 to 3.36). The degree of protection by time since surgery is presented in Table 5.

DISCUSSION

In this study of women with inherited *BRCA1* and *BRCA2* mutations, bilateral oophorectomy is associated with a highly significant reduction in the risk of subsequent breast cancer. The oophorectomy provided substantial risk reduction for 15 years after the operation. Further studies will be necessary to establish if protection persists longer than this. These results confirm findings that have been reported previously in much smaller studies of women with hereditary susceptibility to breast cancer and ovarian cancer.[8-10] The

Table 5. Association Between Oophorectomy Timing and Breast Cancer

Mutation	No. Cases	No. Controls	Unadjusted			Adjusted		
			OR	*P*	95% CI	OR	*P*	95% CI
All, years								
Never	1,388	1,751	1			1		
1-5	31	71	0.47	.0006	0.30 to 0.72	0.47	.0007	0.31 to 0.73
6-10	5	26	0.16	.0007	0.06 to 0.46	0.16	.0006	0.05 to 0.45
11-15	3	8	0.44	.24	0.11 to 1.74	0.44	.24	0.11 to 1.73
15+	12	10	1.30	.58	0.51 to 3.30	1.32	.56	0.52 to 3.36
BRCA1, years								
Never	1,021	1,320	1			1		
1-5	26	58	0.49	.003	0.31 to 0.79	0.50	.004	0.31 to 0.80
6-10	2	20	0.05	.004	0.007 to 0.39	0.05	.004	0.007 to 0.38
11-15	2	6	0.42	.31	0.08 to 2.24	0.40	.28	0.08 to 2.12
15+	8	7	1.20	.76	0.37 to 3.93	1.27	.70	0.38 to 4.17
BRCA2, years								
Never	360	426	1			1		
1-5	5	12	0.38	.10	0.12 to 1.19	0.38	.10	0.12 to 1.19
6-10	3	6	0.50	.33	0.13 to 2.00	0.51	.34	0.13 to 2.03
11-15	1	2	0.50	.57	0.05 to 5.51	0.50	.57	0.05 to 5.51
15+	4	3	1.48	.61	0.33 to 6.66	1.47	.62	0.32 to 6.64

NOTE. Adjusted by oral contraceptive (yes/no) and parity (0, 1, 2, 3,...). All ORs were calculated by conditional logistic regression.
Abbreviation: OR, odds ratio.

results of these studies support the hypothesis that estrogen deprivation reduces the risk of both sporadic breast cancer and hereditary breast cancer. This result was somewhat unexpected, given that the majority of *BRCA1*-associated breast tumors are estrogen-receptor negative,[11] but there are several other hormonally-related modifiers of breast cancer risk that have been identified in *BRCA1* carriers.[12] For example, the risk of breast cancer has been reported to be modestly increased by the use of oral contraceptives,[13] and the risk of contralateral breast cancer is greatly reduced by tamoxifen.[7,14]

In our study, the reduction in breast cancer risk appeared to be greatest for *BRCA1* mutation carriers who underwent oophorectomy before age 40, although a protective effect was also observed for *BRCA1* carriers who were older than this at the time of surgery. A lesser magnitude in risk reduction was seen for *BRCA2* carriers. It is likely that the smaller overall effect in *BRCA2* carriers is because of their later age of diagnosis, and consequently, on average, a greater period of time had elapsed between oophorectomy and breast cancer for *BRCA2* carriers than for *BRCA1* carriers (10.5 years for *BRCA2* carriers versus 7.2 years for *BRCA1* carriers). Thirty-one percent of the *BRCA2* carriers, who had an oophorectomy, underwent this procedure 15 years or more before breast cancer, compared with 21% of *BRCA1* carriers. However, in the 15-year period following oophorectomy, the level of risk reduction was similar for both mutation subgroups, although the sample size of *BRCA2* carriers was much smaller, and the result was of borderline significance. It is possible that the difference observed in risk of breast cancer following oophorectomy in *BRCA1* versus *BRCA2* carriers might reflect biologic differences in tumorigenesis. The functions of the *BRCA1* and *BRCA2* proteins are closely linked, however, the pathologic characteristics of *BRCA1*- and *BRCA2*-associated breast cancers are distinct and the profile of risk factors are different for the two subgroups.[12,15,16] In general, exogenous hormones appear to have a less profound effect on *BRCA2* carriers than on *BRCA1* carriers. Similar differences are seen with breastfeeding[17] and parity (Cullinane et al, The effect of pregnancy as a risk factor for breast cancer in BRCA1/BRCA2 mutation carriers, manuscript in preparation).

Prophylactic oophorectomy is associated with a low risk of operative complications,[9,18] but can commonly result in the abrupt onset of menopausal symptoms. The long-term complications of early surgical menopause include an increased risk of heart disease[19] and of osteoporosis[20] together with a decline in libido and psychological well-being.[21] Hormone replacement therapy until age 50 is often recommended to prevent these complications. However, hormone replacement therapy has not been found to reduce the risk of cardiovascular disease following natural menopause,[22,23] and it is not yet known to what extent, if at all, hormone replacement diminishes the protective effect of oophorectomy on breast cancer risk (this study is currently underway).

In summary, we found a significant degree of protection against breast cancer offered by surgical oophorectomy in *BRCA1* carriers, and a similar, but nonsignificant reduction in *BRCA2* carriers. The protective effect may be limited to the period of 15 years following the surgery. The strongest effects were observed for early oophorectomies (before 40 years of age) and for early-onset breast cancers (diagnosed before 40 years of age) in *BRCA1* carriers. On the basis of the typically early age of onset of hereditary breast cancers, we recommend that preventive oophorectomy be considered for women with *BRCA1* or *BRCA2* mutations aged 35 and older. This surgery is expected to prevent the majority of ovarian cancers in this high risk group as well.

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Appendix

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