

PROPHYLACTIC OOPHORECTOMY IN CARRIERS OF *BRCA1* OR *BRCA2* MUTATIONS

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ABSTRACT

Background Data concerning the efficacy of bilateral prophylactic oophorectomy for reducing the risk of gynecologic cancer in women with *BRCA1* or *BRCA2* mutations are limited. We investigated whether this procedure reduces the risk of cancers of the coelomic epithelium and breast in women who carry such mutations.

Methods A total of 551 women with disease-associated germ-line *BRCA1* or *BRCA2* mutations were identified from registries and studied for the occurrence of ovarian and breast cancer. We determined the incidence of ovarian cancer in 259 women who had undergone bilateral prophylactic oophorectomy and in 292 matched controls who had not undergone the procedure. In a subgroup of 241 women with no history of breast cancer or prophylactic mastectomy, the incidence of breast cancer was determined in 99 women who had undergone bilateral prophylactic oophorectomy and in 142 matched controls. The length of postoperative follow-up for both groups was at least eight years.

Results Six women who underwent prophylactic oophorectomy (2.3 percent) received a diagnosis of stage I ovarian cancer at the time of the procedure; two women (0.8 percent) received a diagnosis of papillary serous peritoneal carcinoma 3.8 and 8.6 years after bilateral prophylactic oophorectomy. Among the controls, 58 women (19.9 percent) received a diagnosis of ovarian cancer, after a mean follow-up of 8.8 years. With the exclusion of the six women whose cancer was diagnosed at surgery, prophylactic oophorectomy significantly reduced the risk of coelomic epithelial cancer (hazard ratio, 0.04; 95 percent confidence interval, 0.01 to 0.16). Of 99 women who underwent bilateral prophylactic oophorectomy and who were studied to determine the risk of breast cancer, breast cancer developed in 21 (21.2 percent), as compared with 60 (42.3 percent) in the control group (hazard ratio, 0.47; 95 percent confidence interval, 0.29 to 0.77).

Conclusions Bilateral prophylactic oophorectomy reduces the risk of coelomic epithelial cancer and breast cancer in women with *BRCA1* or *BRCA2* mutations. (N Engl J Med 2002;346:1616-22.)

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WOMEN with germ-line *BRCA1* or *BRCA2* mutations have an increased risk of breast and ovarian cancer as compared with the general population.¹⁻³ These women often undergo bilateral prophylactic oophorectomy to reduce the risk of ovarian cancer. Nevertheless, the data on the resulting reduction in the risk of cancer are limited.⁴ Moreover, papillary serous peritoneal cancers, which arise from the same cell lineage as ovarian cancer and are clinically indistinguishable from stage III ovarian cancer,⁵⁻⁷ have been reported in women at high risk who have undergone the procedure.^{8,9} Prophylactic oophorectomy reduces the risk of breast cancer by about 50 percent in both carriers of *BRCA1* mutations and genetically uncharacterized women.¹⁰⁻¹⁴ We determined the incidence of papillary serous peritoneal cancer after prophylactic oophorectomy in women with *BRCA1* or *BRCA2* mutations, as compared with the incidence of any cancer of the coelomic epithelium in women who did not undergo prophylactic oophorectomy. We also investigated whether prophylactic oophorectomy reduces the risk of breast cancer in women with *BRCA1* or *BRCA2* mutations, as we had previously observed in a subgroup of the current study population.¹⁰

METHODS

Study Participants

Women with germ-line, disease-associated *BRCA1* or *BRCA2* mutations who reported having undergone prophylactic oophorectomy were identified from 11 North American and European registries (those of Creighton University, Dana-Farber Cancer Institute, Fox Chase Cancer Center, Georgetown University, the University of Chicago, the University of Pennsylvania, the University of Utah,

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Netherlands Cancer Institute, St. Mary's Hospital, Women's College Hospital, and Yale University). The *BRCA1* or *BRCA2* mutation status of all subjects was confirmed by direct mutation testing, with informed consent, under protocols approved by the human-subjects review boards at each institution. Women with *BRCA1* or *BRCA2* variants of unknown functional importance were excluded. Two samples of women who had undergone prophylactic oophorectomy and matched controls were used to evaluate the effect of prophylactic oophorectomy on the risk of ovarian and breast cancer. Potentially eligible controls were selected to be in the study sample at random and without replacement. One or more controls were selected for inclusion in the study sample if they could be matched to a subject who had undergone prophylactic oophorectomy according to type of mutation (*BRCA1* or *BRCA2*), treatment center, and year of birth (within five years).

Study of Ovarian-Cancer Risk

Women were excluded from the study if they had undergone unilateral oophorectomy or had a history of ovarian cancer (including borderline tumors or tumors of low malignant potential) before undergoing prophylactic oophorectomy. Women were included in the group of subjects studied to determine the risk of ovarian cancer only if their surgery was not performed to treat ovarian cancer. A control was eligible if she had a disease-associated *BRCA1* or *BRCA2* mutation, was alive with both ovaries intact at the time the woman with whom she was matched underwent prophylactic oophorectomy, and had no history of ovarian cancer at the time of the matched subject's prophylactic oophorectomy.

Using these criteria, we identified 259 eligible subjects who had undergone prophylactic oophorectomy and 292 eligible controls. Three hundred twenty-five subjects (59 percent) were related to at least one other person in the sample. The relatedness of 49 subjects (9 percent) was unknown for various reasons, and they were assumed to be unrelated to any other subject.

Study of Breast-Cancer Risk

The criteria for choosing subjects and matched controls for the group studied to determine breast-cancer risk were identical to those for the group studied to determine ovarian-cancer risk, except that subjects who had undergone prophylactic oophorectomy were excluded if they had previously undergone mastectomy or had a history of breast cancer (including carcinoma in situ) at the time of the prophylactic oophorectomy. Controls were excluded if they had undergone prophylactic oophorectomy or had a history of breast cancer at the time of the matched subject's prophylactic oophorectomy. Using these criteria, we identified 99 subjects who had undergone prophylactic mastectomy and 142 controls.

Data Collection

Enrollment and follow-up at each center were undertaken without regard to surgical status. Information on vital status and the occurrence of cancer was obtained from medical records, telephone interviews, self-administered questionnaires, or a combination of these. For women who had died since their entry into the study, we reviewed medical records and family-history reports to establish the presence or absence of cancer and to verify that they had died. Self-reported reproductive histories and histories of various types of exposure, including hormone use, smoking, and alcohol consumption, were obtained by questionnaire. Occurrences of cancer after surgery were verified by a review of medical records, operative notes, pathology reports, or a combination of these.

Statistical Analysis

Cox proportional-hazards models were used to estimate differences in the incidence of cancer according to whether the woman had undergone prophylactic oophorectomy, with use of Stata software (release 6). A robust variance-covariance estimation method¹⁵

was used to correct for nonindependence of observations among related subjects. Subjects who had undergone prophylactic oophorectomy and controls were followed from the date of the subject's prophylactic oophorectomy until the occurrence of the first cancer or until censoring. A diagnosis of cancer derived from the coelomic epithelium (in the ovary or peritoneum) was the primary end point in the group studied to determine the risk of ovarian cancer. Observations were censored as of the date when a subject died or was lost to follow-up, or the date of last contact if neither of these events occurred. In the group studied to determine the risk of breast cancer, the primary end point was the first diagnosis of an invasive breast cancer or a ductal carcinoma in situ. Observations were censored as of the date on which the subject received a diagnosis of ovarian cancer or primary peritoneal carcinoma, underwent prophylactic mastectomy, died, or was lost to follow-up, or the date of last contact if none of these events occurred.

RESULTS

Ovarian Cancer

Subjects who underwent prophylactic oophorectomy and controls were matched with respect to *BRCA1* and *BRCA2* status, year of birth, age at the time the subject underwent prophylactic oophorectomy, and the center where the surgery was performed. Subjects who underwent prophylactic oophorectomy were significantly more likely than controls to have received hormone-replacement therapy (47.9 percent vs. 19.9 percent, $P < 0.001$), which is prescribed for symptoms of menopause after oophorectomy (Table 1).

Of 259 subjects who underwent prophylactic oophorectomy, 8 (3.1 percent) received a diagnosis of ovarian cancer or papillary serous peritoneal cancer at or after oophorectomy, as compared with 58 of 292 controls (19.9 percent) (Table 1). Of the eight cancers in the subjects who underwent prophylactic oophorectomy, six were stage I ovarian cancers that were diagnosed at the time of surgery. Two cases of papillary serous peritoneal cancer were diagnosed 3.8 and 8.6 years after surgery. Neither breast nor ovarian cancer developed in 185 of the 259 subjects who underwent prophylactic oophorectomy (71.4 percent) during follow-up, as compared with 153 of 292 controls (52.4 percent, $P < 0.001$). The average length of follow-up after the subject underwent prophylactic oophorectomy was 8.2 years for those undergoing surgery and 8.8 years for the controls ($P = 0.54$). One hundred thirty-six subjects who underwent prophylactic oophorectomy (52.5 percent) and 124 controls (42.5 percent) were followed for at least five years after the surgery in the subject in the oophorectomy group. The hazard ratio for cancer of the coelomic epithelium after prophylactic oophorectomy was 0.04 (95 percent confidence interval, 0.01 to 0.16) (Table 2).

To test whether the point estimate of risk reduction was biased by the use of the date of ascertainment rather than the date of genetic testing, we performed analyses in which the follow-up time was determined from the date of genetic testing to the date of diag-

TABLE 1. CHARACTERISTICS OF THE GROUP STUDIED TO DETERMINE THE RISK OF OVARIAN CANCER.*

CHARACTERISTIC	PROPHYLACTIC OOPHORECTOMY (N=259)	CONTROLS (N=292)	P VALUE†
Age at time of surgical subject's oophorectomy — yr			0.15
Mean	42.0	40.9	
Range	21.2–74.8	19.6–79.1	
Parity ≥1 — no. (%)	225 (86.9)	238 (81.5)	0.10
No. of live births			0.47
Mean	2.7	2.6	
Range	1–9	1–7	
Use of oral contraceptives at any time — no. (%)	194 (74.9)	199 (68.2)	0.16
Use of hormone-replacement therapy at any time — no. (%)	124 (47.9)	58 (19.9)	<0.001
<i>BRCA1</i> mutation — no. (%)	219 (84.6)	240 (82.2)	0.49
<i>BRCA2</i> mutation — no. (%)	42 (16.2)	52 (17.8)	0.82
Years of follow-up			0.47
Mean	8.2	8.8	
Range	0.05–47.9	0.02–46.2	
Post-oophorectomy ovarian or papillary serous peritoneal cancer — no. (%)	2 (0.8)	58 (19.9)	<0.001
Age at diagnosis — yr			0.50
Mean	54.9	50.3	
Range	48.9–61.0	30.1–73.2	
Follow-up time to diagnosis — yr			0.65
Mean	6.2	9.2	
Range	3.8–8.6	0.05–42.8	
Ovarian cancer diagnosed at oophorectomy — no. (%)	6 (2.3)	NA	—
Age at diagnosis — yr			—
Mean	46.9	NA	
Range	33.6–60.5	NA	
Subjects with censored observations — no. (%)‡	185 (71.4)	153 (52.4)	<0.001
Age at time of censoring — yr			0.21
Mean	48.2	46.7	
Range	28.0–85.3	29.6–84.8	

*NA denotes not applicable.

†P values for the comparison of subjects who underwent prophylactic oophorectomy and controls were calculated by Fisher's exact test for discrete variables and the Wilcoxon rank-sum test for continuous variables.

‡Observations were censored after the date of the subject's death, loss to follow-up, or last contact.

nosis of ovarian cancer or censoring in the 450 subjects for whom the date of genetic testing was known. Prophylactic oophorectomy occurred five or more years before testing in 203 women (45 percent), one to five years before testing in 116 women (26 percent), within one year before or after testing in 91 women (20 percent), and one or more years after testing in 40 women (9 percent). This analysis produced a hazard ratio of 0.02 (95 percent confidence interval, 0.01 to 0.14), which was nearly identical to that found when the follow-up time was calculated from the date of surgery.

The pathology records of the two women in whom papillary serous peritoneal cancer developed showed no evidence of ovarian cancer at the time of prophylactic oophorectomy.

The time from oophorectomy to the diagnosis of papillary serous peritoneal cancer was 3.8 years in the case of one woman and 8.6 years in the other. No cases of papillary serous peritoneal cancer were diagnosed in controls with intact ovaries.

All six women in whom ovarian cancer was diagnosed at the time of prophylactic oophorectomy had stage I cancers. Among 37 control women who had ovarian cancer for which the stage was known, 11 percent had stage I cancer, 16 percent had stage II, 65 percent had stage III, and 9 percent had stage IV.

Breast Cancer

In the subgroup of 241 subjects in which the incidence of breast cancer was studied, those who un-

TABLE 2. EFFECT OF PROPHYLACTIC OOPHORECTOMY ON THE RISK OF OVARIAN AND BREAST CANCER, ACCORDING TO SELECTED VARIABLES.*

VARIABLE	OVARIAN OR PAPILLARY SEROUS PERITONEAL CANCER		BREAST CANCER	
	NO.	HAZARD RATIO (95% CI)	NO.	HAZARD RATIO (95% CI)
All subjects	551	0.04 (0.01–0.16)	241	0.47 (0.29–0.77)
Age at oophorectomy†				
<35 yr	124	No events	76	0.39 (0.15–1.04)
35–50 yr	348	0.03 (<0.01–0.20)	146	0.49 (0.26–0.90)
≥50 yr	79	0.11 (0.02–0.76)	19	0.52 (0.10–2.70)
Personal history of breast cancer				
Yes	200	—‡	NA	—
No	351	0.06 (0.01–0.25)	NA	—
Length of follow-up				
<5 yr	304	0.05 (0.01–0.34)	120	0.45 (0.21–0.95)
5–10 yr	103	0.13 (0.02–0.93)	52	0.68 (0.22–2.11)
>10 yr	144	No events	69	0.51 (0.24–1.07)
Parity				
≥1	461	0.04 (0.01–0.18)	204	0.45 (0.27–0.76)
0	90	—‡	35	0.58 (0.12–2.77)
Age at menarche§				
≤12 yr	230	0.05 (0.01–0.37)	95	0.61 (0.29–1.30)
>12 yr	264	0.03 (<0.01–0.23)	122	0.40 (0.21–0.75)
Age at first live birth¶				
<30 yr	376	0.04 (0.01–0.17)	172	0.49 (0.30–0.82)
≥30 yr	70	—‡	27	0.62 (0.08–4.69)

*CI denotes confidence interval, and NA not applicable.

†For controls, the age at oophorectomy was the age at the time of prophylactic oophorectomy in the subjects with whom they were matched.

‡No cases of coelomic epithelial cancer occurred in this group.

§Data were missing for 57 subjects in the ovarian-cancer study and 24 subjects in the breast-cancer study.

¶Data were missing for 15 subjects in the ovarian-cancer study and 5 subjects in the breast-cancer study.

derwent prophylactic oophorectomy were followed for an average of 10.7 years after surgery, and the controls were followed for an average of 11.9 years after the time of the matched subject's prophylactic oophorectomy (Table 3). The length of follow-up was at least five years for 51 of 99 subjects who underwent oophorectomy (51.5 percent) and for 70 of 142 controls (49.3 percent). There were no statistically significant differences between subjects and controls in mean follow-up time, parity, age at delivery of a first live-born child, and age at menarche. There were statistically significant differences between surgical subjects and controls in the rate of oral-contraceptive use (78.8 percent vs. 65.5 percent, $P=0.02$), the rate of use of hormone-replacement therapy (75.8 percent vs. 21.8 percent, $P<0.001$), and the number of subjects with censored observations (78.8 percent vs. 45.1 percent, $P<0.001$).

Twenty-one of 99 subjects who underwent prophylactic oophorectomy (21.2 percent) and 60 of 142 controls (42.3 percent) received a diagnosis of

breast cancer after the time of the surgical subject's prophylactic oophorectomy (hazard ratio, 0.47; 95 percent confidence interval, 0.29 to 0.77) (Table 2). The subjects who underwent prophylactic oophorectomy were significantly older than the controls at the time of diagnosis (52.5 vs. 46.7 years, $P=0.03$). The mean time to the diagnosis of breast cancer after prophylactic oophorectomy was 11.4 years for subjects who underwent prophylactic oophorectomy and 8.0 years for controls ($P=0.09$). Only the first primary breast cancer was considered in our risk-reduction analyses, but a second primary breast cancer developed in five subjects. These results confirm our previous report¹⁰ that the risk of breast cancer is substantially reduced after prophylactic oophorectomy.

DISCUSSION

In this group of subjects, bilateral prophylactic oophorectomy reduced the risk of cancer of the coelomic epithelium associated with *BRCA1* or *BRCA2* mutations by 96 percent and the risk of breast can-

TABLE 3. CHARACTERISTICS OF THE GROUP STUDIED TO DETERMINE THE RISK OF BREAST CANCER.

CHARACTERISTIC	PROPHYLACTIC OOPHORECTOMY (N=99)	CONTROLS (N=142)	P VALUE*
Age at time of surgical subject's oophorectomy — yr			0.20
Mean	40.1	38.9	
Range	21.3–66.4	18.6–69.9	
Parity ≥ 1 — no. (%)	87 (87.9)	121 (85.2)	0.70
No. of live births			0.37
Mean	2.9	2.7	
Range	1–7	1–7	
Use of oral contraceptives at any time — no. (%)	78 (78.8)	93 (65.5)	0.02
Use of hormone-replacement therapy at any time — no. (%)	75 (75.8)	31 (21.8)	<0.001
<i>BRCA1</i> mutation — no. (%)	83 (83.8)	121 (85.2)	0.86
<i>BRCA2</i> mutation — no. (%)	18 (18.2)	21 (14.8)	0.48
Years of follow-up			0.37
Mean	10.7	11.9	
Range	0.17–42.8	0.34–42.5	
Post-oophorectomy breast cancer — no. (%)†	21 (21.2)	60 (42.3)	0.005
Age at diagnosis — yr			0.03
Mean	52.5	46.7	
Range	33.8–74.6	29.2–70.3	
Follow-up time to diagnosis — yr			0.09
Mean	11.4	8.0	
Range	1.6–38.7	0.51–23.0	
Subjects with censored observations — no. (%)‡	78 (78.8)	64 (45.1)	<0.001
Age at time of censoring — yr			0.32
Mean	47.5	46.0	
Range	29.8–79.4	30.6–84.8	

*P values for the comparison of subjects undergoing prophylactic oophorectomy and controls were calculated by Fisher's exact test for discrete variables and the Wilcoxon rank-sum test for continuous variables.

†Only first breast cancers are included.

‡Observations were censored after the date of the subject's death, loss to follow-up, or last contact.

cer by 53 percent. When the upper bound of the 95 percent confidence interval of the hazard ratio was taken as a conservative estimate, prophylactic oophorectomy reduced the risk of cancer of the coelomic epithelium associated with *BRCA1* or *BRCA2* mutations by approximately 85 percent and the risk of breast cancer by approximately 25 percent.

Struewing et al.⁹ reported the results of prophylactic oophorectomy in an analysis of 12 large families with a strong history of breast and ovarian cancer, but without information on *BRCA1* or *BRCA2* mutation status. Two cases of intraabdominal carcinomatosis were noted after prophylactic oophorectomy in 28 women who were first-degree relatives of patients with ovarian cancer, as compared with eight cases of ovarian cancer in 346 women who were first-degree relatives of patients with ovarian cancer and who had not undergone oophorectomy. These results were suggestive of a protective effect of oophorecto-

my, but the sample was not large enough to demonstrate a statistically significant effect of prophylactic oophorectomy on the risk of ovarian cancer.

In our study, six women were found to have ovarian cancer at the time of prophylactic oophorectomy, all of whom had stage I disease. Since only 11 percent of ovarian cancers in the control women were stage I, prophylactic oophorectomy may aid in the identification of early-stage, curable ovarian cancer in women with *BRCA1* or *BRCA2* mutations.

Our study provides some information about the timing of prophylactic oophorectomy relative to the childbearing years. The mean age at the diagnosis of ovarian cancer in our entire data set (including women who were not part of the present study) was 50.8 years (range, 30 to 73 years); this finding supports the practice of performing prophylactic oophorectomy in carriers of *BRCA1* or *BRCA2* mutations as soon as feasible after childbearing is completed. Very

early prophylactic oophorectomy is probably not required to prevent ovarian cancer in most women with *BRCA1* or *BRCA2* mutations.

The primary negative consequence of prophylactic oophorectomy in premenopausal women is premature menopause, which may be associated with increased risks of osteoporosis and cardiovascular disease.^{16,17} Hot flashes, vaginal dryness, sexual dysfunction, sleep disturbances, and cognitive changes associated with menopause may affect the quality of life. However, the risk is balanced by the morbidity and mortality associated with breast and ovarian cancer in carriers of *BRCA1* or *BRCA2* mutations, and these symptoms may be managed by hormonal or nonhormonal medications.

Surveillance has not been shown to reduce the proportion of ovarian cancers diagnosed in late stages or to affect mortality, which is estimated at 80 percent at five years for stage III disease. Oral-contraceptive use was associated with decreased ovarian-cancer risk in one study,¹⁸ but not in another.¹⁹ Because of these conflicting reports, recommending the use of oral contraceptives to reduce the risk of ovarian cancer is problematic. Tubal ligation may also reduce ovarian-cancer risk in carriers of *BRCA1* (but not the *BRCA2*) mutations,²⁰ but its reported efficacy is not nearly as great as that of prophylactic oophorectomy.

There are a number of limitations to this study. The widespread use of prophylactic oophorectomy in carriers of *BRCA1* or *BRCA2* mutations would have made a randomized trial — the ideal type of study — difficult to perform. A prospective cohort design would also be preferred, but it would limit the availability of results for years. Our matched study design corrects for many of the limitations of a retrospective cohort design. In addition, the present data support the common recommendation that women with *BRCA1* or *BRCA2* mutations should undergo prophylactic oophorectomy once they have completed childbearing.

On the basis of the results of our study, we advocate prophylactic oophorectomy to reduce the risk of ovarian and breast cancer in women with *BRCA1* or *BRCA2* mutations. In deciding whether to undergo the procedure, a woman should take into account how long she wishes to maintain fertility, and she should receive counseling about the risks and benefits of prophylactic oophorectomy. The decision should also be made with the knowledge that current surveillance regimens have not been shown to affect the incidence of late-stage ovarian cancer. Although opinion is divided on the use of hormone-replacement therapy after prophylactic oophorectomy, the decision to use estrogens should be based on a consideration of symptoms that affect future health and the quality of life. Some centers routinely recommend hormone-

replacement therapy after prophylactic oophorectomy until the age of 50 years, and many women consider prophylactic oophorectomy unacceptable without this option.

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APPENDIX

The following investigators were members of the PROSE Study Group: University of Pennsylvania — J. Coyne, C. Punzalan, T. Rebbeck, and B. Weber; Creighton University — C. Snyder, H.T. Lynch, and P. Watson; Dana-Farber Cancer Institute — J.E. Garber and H. Gray; Fox Chase Cancer Center — J. Costalas and M.B. Daly; Georgetown University — A. Dialino-Felix, C. Isaacs, and A. Pinto; Netherlands Cancer Institute — M. van Beurden, H. Klaren, and L. van't Veer; Royal Marsden Hospital — R. Eeles and K. Bishop; St. Mary's Hospital — G. Evans and A. Shenton; University of Chicago — S. Cummings, O. Olopade, and M. Roark; University of Utah — L. Cannon-Albright, S.L. Neuhausen, and L. Steele; Women's College Hospital — S.A. Narod and K. Metcalfe; and Yale University — E. Matloff.

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