Salpingo-oophorectomy and the Risk of Ovarian, Fallopian Tube, and Peritoneal Cancers in Women With a *BRCA1* or *BRCA2* Mutation

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Context Women with *BRCA1* or *BRCA2* mutation are often advised to undergo preventive oophorectomy. The effectiveness of this intervention has not been prospectively evaluated in a large cohort.

Objectives To estimate the incidence of ovarian, fallopian tube, and primary peritoneal cancer in women who carry a deleterious mutation in *BRCA1* or *BRCA2*. To estimate the reduction in risk of these cancers associated with a bilateral prophylactic salpingo-oophorectomy.

Design, Setting, and Participants Women known to carry a *BRCA1* or *BRCA2* mutation were identified from an international registry between 1992 and 2003. A total of 1828 carriers at 1 of 32 centers in Canada, the United States, Europe, and Israel completed questionnaires at baseline and follow-up. Participants were observed from the date of study entry until: diagnosis of ovarian, fallopian tube, or peritoneal cancer; death; or the date of the most recent follow-up.

Intervention Participants were divided into women who had undergone bilateral prophylactic oophorectomy and those who had not.

Main Outcome Measure The incidence of ovarian, peritoneal, and fallopian tube cancer was determined by survival analysis. The risk reduction associated with prophylactic salpingo-oophorectomy was evaluated by a time-dependent survival analysis, adjusting for covariates.

Results After a mean follow-up of 3.5 years, 50 incident ovarian, fallopian tube, and peritoneal cancer cases were reported in the cohort. Of the 1828 women, 555 (30%) underwent a bilateral prophylactic salpingo-oophorectomy prior to study entry, 490 (27%) underwent the procedure after entering the study, and 783 (43%) did not undergo the procedure. There were 32 incident cancers diagnosed in women with intact ovaries (1015/100 000 per year). Eleven cancer cases were identified at the time of prophylactic oophorectomy and 7 were diagnosed following prophylactic oophorectomy (217/100 000 per year). The estimated cumulative incidence of peritoneal cancer is 4.3% at 20 years after oophorectomy. The overall (adjusted) reduction in cancer risk associated with bilateral oophorectomy is 80% (multivariate hazard ratio=0.20; 95% confidence interval, 0.07-0.58; $P=.003$).

Conclusion Oophorectomy is associated with reduced risk of ovarian and fallopian tube cancer in high-risk women, although there is a substantial residual risk for peritoneal cancer in *BRCA1* and *BRCA2* mutation carriers following prophylactic salpingo-oophorectomy.

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Women with a deleterious mutation in the *BRCA1* or *BRCA2* gene have a high lifetime risk of ovarian cancer (range, 15%-54%).[1-5] Mutations in either of these genes increase susceptibility to cancers of the ovary, fallopian tube, and peritoneum. It is difficult to distinguish between these 3 forms of cancer

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because the clinical symptoms are similar and because the pathological appearance of the 3 tumor types is almost identical. It is important to generate risk estimates separately for peritoneal cancer for *BRCA1* and *BRCA2* carriers after oophorectomy because this end point is an indicator of the effectiveness of preventive surgery. The level of cancer risk reduction associated with prophylactic oophorectomy has been estimated to be as high as 95%. However, most of the studies to date that have evaluated the risk of ovarian, peritoneal, and fallopian tube cancer have used either historical or cross-sectional designs,[1-5] and these are subject to bias. In this prospective study, we estimate the absolute risks for developing ovarian, fallopian tube, and peritoneal cancers in an international cohort of *BRCA1* and *BRCA2* mutation carriers. The risk reduction associated with prophylactic salpingo-oophorectomy is then estimated after adjustment for a number of cofactors.

METHODS

Study Population

Eligible study participants were women at 1 of 32 centers in Canada, the United States, Europe, and Israel who carry a deleterious *BRCA1* or *BRCA2* mutation. All participants provided written informed consent for genetic testing and for participating in the prospective study. The ethics committees of all participating centers have approved the study. In most cases, genetic testing was offered initially to women who were affected either by breast 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, both affected and unaffected. In some cases, mutation testing was offered directly to unaffected women when no affected family member was available for testing. The criteria for genetic testing varied from center to center, but all participating facilities offered testing to both affected and unaffected women. Mutation detection was performed using a range of techniques, but all abnormal nucleotide sequences were confirmed by the direct sequencing of deoxyribonucleic acid. A woman was eligible for the study when the molecular analysis established that she was a mutation carrier. She was then asked to participate in this prospective study and to complete a baseline questionnaire. This study deals only with women who were free of ovarian cancer at the time of genetic testing. All study participants received genetic counseling and all received their genetic test result prior to study entry. Participants were enrolled in the study from 1992 to 2003. The majority of participants completed the baseline questionnaire at the time of genetic testing or within 1 year of receiving their result. This is a dynamic cohort with ongoing accrual, and therefore, the lengths of follow-up varied from individual to individual. Participants completed a baseline questionnaire and at least 1 follow-up questionnaire, a minimum of 2 years following the baseline questionnaire. The baseline and follow-up questionnaires requested information regarding reproductive history, surgical history (including preventive oophorectomy and mastectomy), and screening practices for breast and ovarian cancer. Questions about exposures to birth control pills and hormone therapy were also included. Follow-up questionnaires were either mailed to each study participant to complete and return, or were administered over the telephone by a genetic counselor or a research assistant at each center.

Participants were excluded if they were diagnosed with ovarian, fallopian tube, or peritoneal cancer prior to the baseline questionnaire. However, participants who had a diagnosis of breast cancer before study entry were not excluded. Participants who had only 1 ovary removed prior to study entry were considered to be at risk for ovarian cancer.

Participants were followed from the date of completion of the baseline questionnaire or age 30 (whichever was later). The members of the cohort were followed from study entry to: (1) the date of completion of the follow-up questionnaire; (2) the development of ovarian, peritoneal, or fallopian tube cancer; (3) age 75 years; or (4) death. Study participants were divided into those who had undergone oophorectomy before the completion of the questionnaire and those who had both ovaries intact at study entry. Women who elected to have an oophorectomy after the questionnaire was completed were transferred from the first cohort to the second cohort at the date of surgery in the survival analysis.

A total of 2891 eligible participants were identified at the 32 centers. We received information regarding 2171 of these (75%). There were 135 women who declined to participate in the follow-up study. Fourteen women had died, but details of the cause of death were not known and these cases were excluded. Another 194 women were excluded because of missing data or loss to follow-up. After exclusions, the study population consisted of 1828 women (63% of the total).

All ovarian, fallopian tube, and peritoneal cancers that were diagnosed in the cohort during the follow-up period were confirmed by review of medical records and/or pathology reports. Age and cause of death of participants who died during the follow-up period were determined from the medical records. The pathology reports were reviewed in order to correctly assign the diagnosis of ovarian, fallopian tube, or primary peritoneal cancer. The diagnosis of primary fallopian tube cancer was made when the tumor predominantly involved the fallopian tube. The diagnosis of primary peritoneal carcinoma was based on the criteria of the Gynecology Oncology Group[6]: (1) both ovaries are of normal size; (2) extra-ovarian involvement is greater than the involvement on the surface of either ovary; (3) the ovarian component was nonexistent (or the ovaries had been removed previously); or (4) the cytological characteristics were of the serous type. All cases of serous peritoneal cancer diagnosed after prophylactic oophorectomy were considered to be primary peritoneal cancer. A single case of primary peritoneal cancer was diagnosed in a woman with intact ovaries. She had ovaries of normal size with microscopic tumor ovarian involvement.

She had metastatic serous papillary cancer in the omentum and throughout the peritoneum. Stage was defined using 1988 International Federation of Gynecology and Obstetrics criteria[7] based on the clinical and the pathologic reports.

Statistical Analysis

Initially, the overall incidence of ovarian, fallopian tube, and peritoneal cancer was determined in the entire cohort by survival analysis, using the Kaplan-Meier method. For this estimate, all women were considered to be at risk and all incident cancers were included. Second, we estimated the actuarial risks of ovarian, fallopian tube, and peritoneal cancer in the subgroups of women with both ovaries intact and following oophorectomy. Women in the first group were observed from study entry until they were diagnosed with cancer, underwent an oophorectomy, death, or completion of the follow-up questionnaire. The second group of women were followed from the date of oophorectomy or study entry (whichever came last) until they were diagnosed with cancer, death, or completion of the follow-up questionnaire. This subcohort only included women who were free of cancer at the time of oophorectomy. Women who underwent an oophorectomy during the study follow-up period were transferred from the first group to the second group at that time (see below).

The derived incidence rates for women with intact ovaries were then used to estimate the penetrance of ovarian cancer to age 75 years. Penetrance estimates for *BRCA1* and *BRCA2* carriers were derived by applying the calculated age-specific rates to a theoretical cohort of women from the age of 30 years until age 75 years. These rates were applied both for women with and without breast cancer.

The expected numbers of ovarian cancers for each subgroup were then calculated using age- and country-specific incidence rates derived from the IARC Scientific Publication *Cancer Incidence in Five Continents*.[8] Expected numbers were calculated separately for each of the 6 countries, by 5-year age groupings beginning at age 30 years and ending at age 75 years. The observed women-years of risk in each age-country category were multiplied by the expected cancer incidence to estimate the total expected number of cancers for each category. The standardized incidence ratios were determined by summing the observed and expected numbers of cancers. Statistical significance was evaluated using the Poisson test.

The Cox proportional hazards model was used to determine the hazard ratio (HR) of cancer in women after oophorectomy compared with women with 2 ovaries intact. Oophorectomy was included in the model as a time-dependent covariate. The HR was adjusted for age at study entry, oral contraceptive use (ever vs never), breastfeeding (number of months), parity (0, 1, 2, 3, 4+), mutation (*BRCA1* or *BRCA2*), and country of origin. The 8 women with a mutation in both genes were excluded from these analyses. For purposes of this comparison, the 11 women in the cohort in whom ovarian cancer was identified at the time of prophylactic oophorectomy were considered to be at risk for ovarian cancer from the date of the baseline questionnaire until the date of the oophorectomy, and were withdrawn from the cohort at that time (ie, their cancer was assigned to neither subgroup).

RESULTS

There were 1828 women in the cohort who completed a baseline questionnaire and who provided follow-up information. The mean age of the cohort at study entry was 47.3 years (range, 30-74 years); 1380 participants (75.5%) carried a *BRCA1* mutation, 440 (24.1%) carried a *BRCA2* mutation, and 8 participants (0.4%) carried both a *BRCA1* and *BRCA2* mutation.

Of the 1828 participants, 555 (30.4%) participants had a prophylactic bilateral salpingo-oophorectomy prior to study entry and 1273 participants had not had bilateral salpingo-oophorectomy. Of the 1273 women who had intact ovaries, 490 (38.5%) underwent an oophorectomy during the follow-up period. The women who had an oophorectomy were older than women who had intact 2 ovaries by a mean of 3.8 years (45.1 years vs 48.9 years; $P<.001$). There were 834 out of 1045 women (80%) who had undergone oophorectomy who carried a *BRCA1* mutation, compared with 546 out of 783 (70%) of women with intact ovaries ($P<.001$). However, the women who did and who did not have ooophorectomies were similar with respect to past history of breast cancer, parity, and the use of oral contraceptives and hormone therapy. The characteristics of the participants are presented in **TABLE 1**.

The women were observed for a mean of 3.5 years. Among the women with intact ovaries, 32 cancers were observed (29 ovarian, 2 fallopian tube, and 1 primary peritoneal cancer). The mean age at diagnosis was 53.8 years (range, 34-72 years). Twenty-nine cancers developed in *BRCA1* mutation carriers (mean age 53.5 years) and 3 cancers developed in *BRCA2* mutation carriers (mean age 57.3 years). Twenty-four (75%) of the women had a personal history of breast cancer.

During the follow-up period, 490 women underwent a prophylactic oophorectomy. Of these women, 11 (2.2%) were diagnosed with occult cancer at the time of preventive surgery (**TABLE 2**). Seven of the cancers were classified as ovarian and 3 were diagnosed as primary fallopian tube carcinoma. In 1 case, the peritoneal washings were positive for carcinoma but no source of cancer was found in either the ovaries or fallopian tubes. The mean age at the time of prophylactic surgery for women diagnosed with occult cancer was 47.7 years (range, 38-68 years). The youngest cancer diagnosed at prophylactic oophorectomy was at age 38 years; eight of the 11 cases were diagnosed prior to age 50 years. Only 1 of the 11 patients had died of cancer (4 years after diagnosis of stage I disease). The other 10 patients are alive after a mean of 2.2 years (range, 1-5 years).

Seven women were diagnosed with primary peritoneal cancer following preventive oophorectomy (mean age 51.1 years), 6 were *BRCA1* mutation carriers, and 1 was a *BRCA2* mutation carrier. Four underwent a bilateral salpingo-oophorecotomy and 3 had their

ovaries, fallopian tubes, and uterus removed. A mean of 5.3 years had elapsed between preventive surgery and cancer diagnosis (median 3 years; range, 1-20 years) (TABLE 3). Four of these 7 women have died of their disease (average survival 3 years).

The risks for ovarian, fallopian tube, and primary peritoneal cancers for women with intact ovaries, by age and mutation type, are presented in TABLE 4. The highest incidence rate was observed for *BRCA1* mutation carriers between the ages of 60 years and 70 years (annual risk, 3505/100 000). The risk of peritoneal cancer following oophorectomy was 217 per 100 000 per year (TABLE 5). The risk was modestly higher for *BRCA1* mutation carriers (230/100 000) than for *BRCA2* mutation carriers (167/100 000) but the difference was nonsignificant. The observed numbers of cancers by age group and mutation type were then compared with the expected numbers based on cancer registry information in *Cancer Incidence in Five Continents*.[8] The ratios of observed

Table 1. Characteristics of Participants in the Cohort Study

	No Oophorectomy (n = 783)	Oophorectomy at Baseline (n = 555)	Oophorectomy During Follow-up (n = 490)	All Participants (n = 1828)
Age at baseline, mean (range), y	45.1 (30-74)	51.3 (30-74)	46.3 (30-74)	47.3 (30-74)
Age at prophylactic oophorectomy, mean (range), y		45.2 (13-74)	47.6 (19-76)	46.4 (13-78)
Mutation, No. (%)				
BRCA1	546 (69.7)	460 (82.9)	374 (76.3)	1380 (75.5)
BRCA2	233 (29.8)	94 (16.9)	113 (23.1)	440 (24.1)
Both	4 (0.5)	1 (0.2)	3 (0.6)	8 (0.4)
Follow-up, mean (range), y	3.27 (0.01-9.6)	3.60 (0.1-9.6)	3.75 (0.3-9.8)	3.50 (0.01-9.8)
Previous breast cancer, No. (%)	421 (53.8)	331 (59.6)	366 (54.3)	1018 (55.7)
Age of diagnosis, mean (SD), y	41.3 (9.2)	43.3 (8.3)	41.4 (7.5)	42 (8.5)
Parity, mean (range)	2.0 (0-10)	2.2 (0-8)	2.1 (0-10)	2.1 (0-10)
Oral contraceptive use at baseline				
Ever, No. (%)	516 (66.8)	369 (67.0)	352 (72.1)	1237 (68.3)
Duration, mean (SD), y	5.8 (4.9)	5.3 (4.8)	6.0 (5.0)	5.7 (4.9)

Table 2. Description of Cancers Diagnosed at Prophylactic Oophorectomy

Case No.	Mutation	Age at Prophylactic Oophorectomy, y	Site	Surgical Stage	Previous Breast Cancer	Vital Status and Age at Follow-up, y
1	*BRCA1*	49	Ovary	IIIC	Yes	Alive at 50
2	*BRCA1*	43	Ovary	IIIC	Yes	Alive at 46
3	*BRCA1*	51	Ovary	NA	Yes	Alive at 56
4	*BRCA1*	38	Ovary	IIIC	Yes	Alive at 39
5	*BRCA2*	68	Tubal	IA	Yes	Alive at 69
6	*BRCA1*	45	Malignant cytology	NA	No	Alive at 46
7	*BRCA1*	40	Ovary	IA	Yes	Dead of disease at 44
8	*BRCA2*	51	Tubal	IA	No	Alive at 57
9	*BRCA1*	49	Tubal	IIIC	No	Alive at 51
10	*BRCA1*	45	Ovary	NA	Yes	Alive at 46
11	*BRCA1*	46	Ovary	NA	Yes	Alive at 47

Abbreviation: NA, not available.

Table 3. Description of Primary Peritoneal Cancers Diagnosed Following Prophylactic Oophorectomy

Case No.	Mutation	Age at Prophylactic Oophorectomy, y	Procedure	Age at Cancer Diagnosis, y	Previous Breast Cancer	Vital Status and Age at Follow-up, y
1	*BRCA2*	46	TAH-BSO	49	No	DOD at 52
2	*BRCA1*	44	BSO	45	Yes	DOD at 49
3	*BRCA1*	38	BSO	43	No	DOD at 46
4	*BRCA1*	51	BSO	71	No	Alive at 72
5	*BRCA1*	51	TAH-BSO	55	Yes	Alive at 57
6	*BRCA1*	36	TAH-BSO	38	No	Alive at 40
7	*BRCA1*	55	BSO	57	Yes	DOD at 59

Abbreviations: DOD, dead of disease; TAH-BSO, total abdominal hysterectomy and bilateral salpingo-oophorectomy.

to expected numbers are represented as standard incidence ratios (Table 5). Based on the calculated incidence rates for women with 2 intact ovaries, the penetrance of ovarian cancer was estimated to be 62% to age 75 years for *BRCA1* mutation carriers and 18% to age 75 years for *BRCA2* mutation carriers (FIGURE 1).

The Kaplan-Meier probabilities of ovarian cancer for *BRCA1* mutation carriers with and without intact ovaries are presented in FIGURE 2. A Cox proportional hazards model was then used to estimate the extent of risk reduction associated with prophylactic oophorectomy for *BRCA1* and *BRCA2* carriers combined. The multivariable model also included terms for age, gene, country of origin, past history of breast cancer, oral contraceptive use, breast-feeding, and parity. The crude HR associated with oophorectomy was 0.26 (95% CI, 0.09-0.74). After adjustment for covariates, there was an 80% reduction in risk associated with oophorectomy in this study (HR, 0.20; 95% CI, 0.07-0.58).

COMMENT

We estimate that the risk of ovarian, fallopian tube, and peritoneal cancer is reduced by 80% for *BRCA1* and *BRCA2* mutation carriers who undergo a prophylactic oophorectomy. Ours is the largest prospective study of *BRCA1* and *BRCA2* mutation carriers to date that examines the risks for these cancers in women with and without ovaries. Based on the incidence rates calculated here, we estimate the risk of ovarian cancer to be 62% for *BRCA1* carriers and 18% for *BRCA2* carriers in women up to age 75 with both ovaries intact . The penetrance estimate for *BRCA1* is higher than most previous estimates but it is based on 29 incident cancers and chance may be a factor. However, there are other possible reasons for the high observed rates. Previous estimates have been based on reports of family histories[1-5] and in general, these have not excluded relatives who had undergone an oophorectomy from the at-risk group. Furthermore, patients may have incomplete knowledge about their relatives' cancer histories. In contrast, we have included only confirmed cases of cancer in our study. Second, a high proportion of cancer cases in our study had a previous diagnosis of breast cancer (70%). We found suggestive evidence that the risk of ovarian, fallopian tube, and peritoneal cancer was higher in women with previous breast

Table 4. Annual Risks of Ovarian, Peritoneal, or Fallopian Tube Cancer in *BRCA1* and *BRCA2* Carriers With Intact Ovaries

	BRCA1				*BRCA2*			
Age Group, y	No.	Cancers*	Person-Years	Annual Risk (Per 100 000 Per Year)	No.	Cancers*	Person-Years	Annual Risk (Per 100 000 Per Year)
30-39	346	2	973.2	206	86	0	290.0	0
40-49	328	13	678.2	1918	133	0	385.0	0
50-59	164	9	297.0	3030	79	2	204.0	986.6
60-69	52	4	114.1	3505	38	1	108.0	927.1
70-74	21	1	59.3	1685	8	0	19.7	0
Total	**911**	**29**	2121.9	1367	**344**	**3**	1006.7	298.5

*Eleven cancers diagnosed at prophylactic oophorectomy were excluded.

Table 5. Observed and Expected Numbers of Ovarian, Peritoneal, or Fallopian Tube Cancers in *BRCA* Mutation Carriers Between Ages 31 to 75 Years

	No. of Women	Total Person-Years	Observed Cancers	Total Expected Cancers	Observed Incidence (Per 100 000 Per Year)	Expected Incidence (Per 100 000 Per Year)	Standardized Incidence Ratio	*P* Value*
All	1828	6177	50	1.34	782	21.0	37.3	<.001
BRCA1	1380†	4751	44	0.98	926	20.6	44.9	<.001
BRCA2	440†	1606	6	0.33	373	20.8	17.9	<.001
Breast cancer								
Yes	1018	3503	34	0.84	970	24.1	40.3	<.001
No	810	2893	16	0.49	553	16.9	32.7	<.001
No prophylactic oophorectomy								
All	1262	3152	32	0.55	1015	17.5	58.1	<.001
BRCA1	911†	2122	29	0.36	1367	16.8	81.6	<.001
BRCA2	344†	1005	3	0.18	299	18.1	16.5	<.001
Prophylactic oophorectomy								
All	1034	3221	7	0.76	217	23.5	9.3	<.001
BRCA1	825†	2607	6	0.59	230	22.8	10.1	<.001
BRCA2	205†	600	1	0.14	167	23.9	7.0	<.001

**P* values were calculated by Poisson test.
†Categoric totals differ because numbers of women who are both *BRCA1* and *BRCA2* mutation carriers are not included.

cancer than in women without a history of breast cancer history (HR, 2.0; $P=.07$). This may be a chance finding but it is also possible that there are common risk factors for breast and ovarian cancer, or that some aspect of breast cancer treatment increases the risk of subsequent ovarian cancer. We have recently reported that tamoxifen treatment was associated with a small but nonsignificant increase in the risk of ovarian cancer.[9] In this study, we estimated the risk for ovarian cancer following breast cancer to be 13% at 10 years for *BRCA1* mutation carriers and 7% at 10 years for *BRCA2* mutation carriers.

It is also possible that our risk estimate might be high because we did not obtain a follow-up questionnaire on all women who completed a baseline questionnaire. If there has been preferential reporting of the follow-up status for women who developed ovarian, fallopian tube, or peritoneal cancer, then this might lead to a spurious risk increase. The 1828 participants included our study were similar to the 1064 patients with no follow-up information in terms of age of interview and the proportions with a history of breast cancer or who had previously used oral contraceptives or hormone therapy (data not shown).

The women in our study were tested because of a personal or family history of breast or ovarian cancer. These participants are representative of the women who are referred for genetic testing, but may experience a higher level of cancer risk than unselected women in the general population.

Liede et al[10] examined cancer incidence in a population of Jewish women who were at risk for ovarian cancer in a historical cohort study. They estimated the 10-year risk for *BRCA1* carriers for ovarian, peritoneal, or fallopian tube cancer to be 21% or approximately 2% per year. This is higher than our finding of an annual risk of 1.4% per year in *BRCA1* mutation carriers. Liede et al[10] also estimated the risk of peritoneal cancer to be much higher (20% at 10 years), but their study was completed with a cohort of women with ovaries and it is difficult to diagnose this condition in the presence of intact ovaries. We recorded only a single case of peritoneal cancer among women with intact ovaries vs 7 cases in women following oophorectomy. It is easier to estimate the risk of peritoneal cancer among women after the ovaries have been removed because the problem of misclassification is thereby diminished.

Ovarian cancer risk is age-dependent and age differences may account for variations in the risk estimates for various studies. It is also possible that the risk varies with the actual mutation. In the Liede study,[10] the majority of mutations were the common 185delAG mutation. Recently, Gronwald et al[11] reported significant differences in ovarian cancer risk for each of the 3 founder *BRCA1* mutations in Poland.

Women who carry a mutation in the *BRCA1* gene are asked to consider prophylactic bilateral salpingo-oophorectomy at age 35 or thereabouts, in order to reduce the risk of ovarian, fallopian tube, and breast cancer.[12,13] Our observations support this recommendation. It may be reasonable to wait until a time closer to menopause to prevent ovarian and fallopian tube cancer in *BRCA2* carriers but this delay will diminish the level of protection offered against breast cancer in this subgroup.[12]

We estimate the magnitude of the risk reduction for ovarian, fallopian tube, and peritoneal cancer to be approximately 80%. Previous estimates of the effectiveness of prophylactic oophorectomy have

Figure 1. Penetrance of Ovarian, Fallopian Tube, and Peritoneal Cancer Among Carriers of *BRCA1* and *BRCA2* mutations

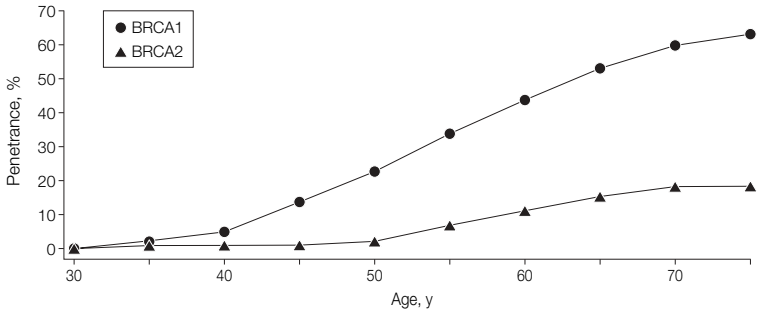
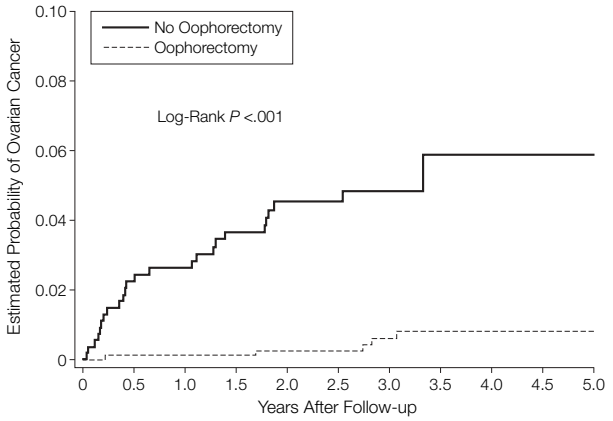


Figure 2. Kaplan-Meier Estimated Probability of Ovarian Cancer Among *BRCA1* Carriers With and Without Intact Ovaries



No. at Risk											
No Oophorectomy	546	513	495	472	439	352	271	180	117	82	59
Oophorectomy	825	817	810	796	758	644	501	360	268	203	162

varied widely from 60% to 95%[14-19] but none of these estimates were based on a large prospective study. Earlier studies were based on family history alone[14,15] or were retrospective studies,[16,17] case-control studies,[18] or small prospective studies.[19]

Early studies did not take into consideration genetic status. Tobacman et al[14] reported peritoneal cancer in 3 of 28 women after prophylactic oophorectomy, and Piver et al[15] reported 6 primary peritoneal cancers in a cohort of 324 high-risk women, occurring from 1 to 27 years after prophylactic oophorectomy. In these 2 studies, all women had a family history of ovarian cancer but none had undergone genetic testing.

Rebbeck et al[16] determined the incidence of ovarian cancer in 259 women who had undergone prophylactic oophorectomy and 292 matched controls that had not undergone the procedure. They reported that prophylactic oophorectomy significantly reduced the risk of ovarian cancer by 96% (HR, 0.04), based on 2 observed cases of papillary serous peritoneal carcinoma, which occurred 4 and 9 years after prophylactic oophorectomy. However, this was not a prospective study and in most cases genetic testing had taken place after the diagnosis of the incident cancer. In a similar study from the Netherlands, Olivier et al[17] reported that 3 of 84 *BRCA1* mutation carriers developed primary peritoneal cancer after oophorectomy. In all 3 cases, the fallopian tubes had been left intact, suggesting that these cases may actually have had tubal origins. Rutter et al[18] identified 5 women with a *BRCA1* mutation who developed peritoneal cancer following oophorectomy. Compared to a cancer-free control group, they estimated the cancer risk reduction associated with bilateral oophorectomy to be 71% (OR=0.29; 95% CI, 0.12-0.73).

In the only other purely prospective study reported to date, Kauff et al[19] reported an HR of 0.25 for breast and gynecologic cancers combined in a cohort of 170 *BRCA* mutation carriers who chose prophylactic surgery, compared with those who were followed by surveillance alone. They estimated the reduction in risk for ovarian, peritoneal, and fallopian tube cancer to be 85%; however, only a single case of cancer was diagnosed following oophorectomy and the risk reduction was not statistically significant. Powell et al[20] reported 2 cases of primary peritoneal cancer after prophylactic salpingo-oophorectomy in a cohort of 67 participants. Both cancers were diagnosed 5 years after surgery.

The women in this study were aware of their genetic status and it is probable that most women underwent regular surveillance for early detection of ovarian cancer by vaginal ultrasound and/or CA-125 blood levels; however, most of the incident cancers were diagnosed after the patients experienced clinical symptoms of ovarian cancer and were discovered at an advanced surgical stage. Three of 7 cancers diagnosed through prophylactic oophorectomy were stage IA.

We identified 11 cancers in 490 women at the time of prophylactic oophorectomy, representing a prevalence of 2.4% of *BRCA1* mutation carriers and 1.8% of *BRCA2* mutation carriers undergoing the operation. The prevalence of occult carcinomas in previous studies of oophorectomy patients varies widely. Comparisons have been hampered by the lack of standardized pathologic exam of the tissue at the time of the surgery. In 1985, Chen et al[21] reported a case of a woman who underwent prophylactic oophorectomy and subsequently died of intra-abdominal carcinomatosis. On retrospective examination of the ovaries, a small focus of adenocarcinoma was found on the ovarian surface. Numerous other authors have also emphasized the need for rigorous pathologic examination.[18,20-24] Among 98 *BRCA* mutation carriers who underwent prophylactic oophorectomy at Memorial Sloan-Kettering Cancer Center, 3 early-stage neoplasms were found (3.1%).[19] Finch et al[24] reported on 7 cancers identified in 159 *BRCA* mutation–positive women (4.4%) at prophylactic oophorectomy and Rebbeck et al[16] reported 6 (2.3%) diagnoses of occult stage I ovarian cancer among 259 women who underwent prophylactic oophorectomy. Powell et al[20] found 6 microscopic ovarian cancers and 1 apparent ovarian cancer among 41 *BRCA* mutation carriers at oophorectomy (17%). It is possible that fewer peritoneal cancers will be diagnosed after oophorectomy if the comprehensive pathology review of the salpingo-oophorectomy specimens is conducted on all patients (undiagnosed cancers at the time of surgery will be considered primary peritoneal cancer when they become clinically apparent).

In order to estimate penetrance in an unbiased fashion, we did not include these cancers detected at prophylactic oophorectomy in the calculation of our incidence rates. For the estimation of rates among women with ovaries intact, women were considered to be at risk until the time of the prophylactic oophorectomy. For the calculation of the rate among women after oophorectomy, we considered women to be at risk from the date of oophorectomy.

We estimate the risk of peritoneal cancer in the 20 years following oophorectomy to be 4.3% or roughly 9 times greater than the ovarian cancer risk in the noncarrier population. On average, the peritoneal cancers were diagnosed 5 years after oophorectomy, but 3 cases were diagnosed within 3 years of surgery. It is possible that these are actually metastases of sub-clinical disease that was present at the time of surgery and that we have overestimated the risk of incident peritoneal cancer. It is currently recommended that removed ovaries and fallopian tubes receive close examination to identify microscopic disease.[24] In the future, it will be important to address the question of whether or not the risk of peritoneal cancer might be reduced by nonsurgical means such as oral contraceptives.

The primary strength of our study is that this is the first large-scale prospective study of ovarian cancer risk in women with *BRCA1* and *BRCA2* mutations. Previous studies have either been very small (and the results nonsignificant) or they used a historical cohort design whereby genetic testing took place after the diagnoses of the incident cancers. Historical cohort studies are subject to bias because women who expe-

rience the end point of interest (ovarian, fallopian tube, or peritoneal cancer) may be more (or less) likely to undergo testing than healthy women because of local genetic testing criteria or high mortality. The mortality experience of women with peritoneal cancer may be even greater than that of ovarian cancer. Our study supports the recommendation for prophylactic oophorectomy as a highly effective means of reducing the risk of ovarian and fallopian tube cancer in *BRCA1* and *BRCA2* carriers. We estimate the magnitude of the risk reduction to be approximately 80% and the residual risk of 4% of peritoneal cancer is not sufficiently high to recommend against the procedure. It is important that both the fallopian tubes and ovaries be removed because either site may be the origin of cancer and both organs should be examined in fine detail to rule out the presence of microscopic disease.[24]

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