

Gynecologic Surgeries and Risk of Ovarian Cancer in Women With BRCA1 and BRCA2 Ashkenazi Founder Mutations: An Israeli Population-Based Case–Control Study

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Background: In the general population, the risk of developing ovarian cancer is reduced in women who have undergone tubal ligation, hysterectomy, or oophorectomy, although peritoneal cancer can arise after bilateral oophorectomy. In studies from genetic screening clinics, women with mutations in the breast and ovarian susceptibility genes BRCA1 and BRCA2 have been found to have a low risk of peritoneal carcinoma in the first years after bilateral oophorectomy. We assessed the level and persistence of reduction of ovarian (including peritoneal) cancer risk after gynecologic surgeries for women who carry BRCA1/2 mutations but were not selected from high-risk clinics. **Methods:** We identified 1124 Israeli women with incident ovarian cancer or primary peritoneal cancer and tested 847 of them for the three Ashkenazi founder mutations. We compared gynecologic surgery history among all case patients, BRCA1 (n = 187) and BRCA2 (n = 64) carrier case patients, and the non-carrier case patients (n = 598) with that in control subjects drawn from a population registry (n = 2396). We estimated ovarian cancer risk (odds ratios [ORs] with 95% confidence intervals [CIs]) after gynecologic surgery in mutation carriers and non-carriers with logistic regression models. **Results:** Eight women with primary peritoneal cancer and 128 control subjects reported a previous bilateral oophorectomy (OR = 0.12, 95% CI = 0.06 to 0.24). Other gynecologic surgeries were associated with a 30%–50% reduced risk of ovarian cancer, depending on the type of surgery, with surgery to remove some ovarian tissue associated with the most risk reduction (OR = 0.34, 95% CI = 0.16 to 0.74). Reduced risks were seen in BRCA1/2 carriers and non-carriers. Age at surgery and years since surgery did not affect risk reductions. **Conclusion:** Both BRCA1/2 mutation carriers and non-carriers have reduced risk of ovarian or peritoneal cancer after gynecologic surgery. The magnitude of the reduction depends upon the type and extent of surgery. [J Natl Cancer Inst 2003;95:1072–8]

Ovarian cancer has the highest case fatality rate of all gynecologic cancers and few preventive or screening options (1). A family history of ovarian cancer is a strong predictor for developing the disease and is often indicative of a pathogenic mutation in one of the breast and ovarian cancer susceptibility genes, BRCA1 and BRCA2 (2,3). Cumulative risk estimates for ovarian cancers in the total population of BRCA1/2 mutation carriers range from 16% to 44% by age 70 (4,5), with estimates for ovarian cancer in high-risk families greater still. In general, women with hereditary ovarian cancer are more likely to have BRCA1 mutations than BRCA2 mutations.

Although prophylactic oophorectomy is now an accepted method of ovarian cancer risk reduction for women at high risk for the disease, primary peritoneal cancers can occur after oophorectomy. Two recent reports (6,7) suggested considerable reduced risk of developing cancers of the ovary or peritoneum after preventive surgery. In a prospective study (6), 170 BRCA mutation carriers were followed for a mean of 2 years after 98 had surgery and 72 chose surveillance without surgery. Among the women who had had surgery, one developed primary peritoneal cancer after the surgery, whereas among the women in the surveillance group, one developed primary peritoneal cancer and four developed ovarian cancer. In a retrospective cohort study (7), an analysis of 551 BRCA mutation carriers assembled from clinics for women with a strong family history of breast or ovarian cancer found that six of 259 (2.3%) women had ovarian cancer at the time of their prophylactic surgery and that two women developed peritoneal cancers during the next 9 years. During the same time, 58 of 292 (20%) women who chose not to have surgery developed ovarian or peritoneal cancer. A study of high-risk Jewish women enrolled in a screening program (8) showed that 21% of BRCA1/2 mutation carriers developed ovarian or peritoneal cancers in 10 years. A potential limitation of these three studies (6–8) is that they predominately involved women from high-risk families, illustrated by their high rates of developing ovarian cancer.

To avoid the limitation associated with use of high-risk families, we have used a population-based design to examine the long-term associations of gynecologic surgeries on ovarian cancer risk among BRCA1/2 mutation carriers and non-carriers. We evaluated the association of prophylactic oophorectomy with ovarian or peritoneal cancer risk in the context of all of the major types of gynecologic surgeries. Using our population-based sample, we studied non-carriers and carriers of the three Ashkenazi founder mutations (185delAG and 5382insC in BRCA1 and 6174delT in BRCA2) to measure the associations of the range of typical gynecologic surgeries on ovarian cancer risk

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and to assess how these associations vary with BRCA1 and BRCA2 mutations.

METHODS

Study Population

The rapid case ascertainment and control selection criteria have been described in previous reports (9–11). Briefly, from March 1, 1994, through June 30, 1999, a nationwide study of ovarian cancer was conducted in Israel. Study staff identified all Jewish women with pathologically confirmed epithelial ovarian cancer or primary peritoneal cancer by weekly telephone inquiries and personal contacts with the chief nurses in the 22 gynecologic departments in Israel. After they were identified, the case patients were followed. After the patient recovered from surgery, the study staff performed the interviews in the hospital. Six percent of the case patients were interviewed during chemotherapy treatment and at home.

Control women were selected from the Israeli Central Population Registry, two per case patient, and were matched for age (within 2 years), area of birth, and place and length of residence in Israel. The study protocol was approved by institutional review boards in Israel and the United States, and participants gave written informed consent. The participation response rate was 79% for case patients and 66% for control subjects.

The case definition included all epithelial ovarian cancers ($n = 1036$) (code 183.0 of the International Classification of Diseases, 9th revision, Clinical Modification) and peritoneal carcinomas ($n = 88$) (code 158.0). The primary peritoneal cancers were counted as post-bilateral oophorectomy cases only if the pathology records clearly indicated that the ovaries removed during a previous surgery were clear of cancer cells. Borderline and germ-cell ovarian tumors were excluded in the analysis because of the possibility of different etiology.

Data Collection

In-person interviews were conducted, and samples for BRCA1 and BRCA2 founder mutation screening were obtained from blood or paraffin-embedded tumor tissue (from the case patients) or by buccal cell collection (from the control subjects), as previously described (9). Most of the case patients were interviewed in the hospital within 4–6 days after their gynecologic surgery. The interview included questions on menstrual, reproductive, medical, and dietary histories. Past gynecologic surgeries were self-reported. Abstraction of medical records of these surgeries was performed and validated for 109 of 275 (40%) of the subjects. Of the 109, 95 (87%) were in agreement. We do not know whether such close agreement would characterize all self-reports of gynecologic surgeries, but close agreement between self-reports and medical records has been reported elsewhere (12,13).

Laboratory Methods

Laboratory procedures to detect the BRCA1 and BRCA2 founder mutations have been described elsewhere (9). Briefly, we used a multiplex polymerase chain reaction assay containing reagents to detect all three founder mutations within one reaction tube, and analyzed the results with an Applied Biosystems model 310 genetic analyzer and Genescan software (Applied Biosystems, Foster City, CA). Founder mutation screening results were obtained from 847 of 891 (95%) of case patients.

Buccal cell collection on the control subjects was initiated midway through the study, and we were able to collect samples from 968 of 2268 control subjects. We successfully tested 790 (81.6%) samples for founder mutations.

Statistical Methods

We compared history of gynecologic surgeries among case patients and control subjects using descriptive statistics and estimated odds ratios (ORs) and the 95% confidence intervals (CIs) from logistic regression models. All analyses were adjusted for age in decades, ethnicity, parity, and oral contraceptive use, unless otherwise noted. In analyses designed to estimate the association with gynecologic surgery in carriers or non-carriers separately, we used as case patients either carriers only or non-carriers only from among the women with ovarian cancer, and as control subjects all the non-diseased women, whether they tested as carriers or non-carriers or were untested, as in our previous report (9). This approach gives unbiased estimates of the effects if the history of gynecologic surgery is independent of carrier status, conditional on other terms in the model (14). The unconditional assumption may not hold, for example, if family history of cancer encouraged gynecologic surgery. By conditioning on family history of cancers of the breast and ovary, we reduce the chance that the independence assumption is materially violated. All statistical tests were two-sided and were performed using SAS version 8.2 software (SAS Institute, Cary, NC) and BMDP Version 1990 Statistical Software (BMDP Software, Los Angeles, CA).

RESULTS

During the study period, 1326 Israeli women were diagnosed with epithelial ovarian cancer or with primary peritoneal cancer. The overall distribution of the histologic subtypes of the ovarian cancers seen in this study was comparable with that reported by the Surveillance, Epidemiology, and End Results (SEER)¹ Program registry of The National Cancer Institute (15). Compared with the proportion of serous ovarian cancers reported by SEER, proportionally more serous ovarian cancers were noted among the Israeli case patients (47% versus 59%). A similar pattern was reported in at least one series of hereditary ovarian cancers (16).

Of the eligible case patients, 1124 (84.8%) were interviewed, and their characteristics are shown in Table 1. Of the 1124 case patients, 88 had ovarian or peritoneal and 18 had fallopian tube primary cancers. More than 70% of the case patients were of Ashkenazi origin, with the remainder of non-Ashkenazi (23.6%) or mixed (5.7%) ancestry. Of the 1124 case patients, 277 were excluded from DNA mutation analysis: 226 case patients did not provide a sample or refused consent for BRCA1/2 testing, and DNA from 51 case patients was of poor quality. Thus, we analyzed DNA from 847 case patients. Of these patients, 187 carried a founder BRCA1 mutation, 64 carried a founder BRCA2 mutation, two carried a founder mutation in both genes, and 598 were non-carriers of the founder mutations (Table 1). As shown in a previous report (9), there were no statistically significant differences in age at diagnosis or ethnic origin between those who were tested for the founder mutations and those who were not.

We first estimated the association of a reported bilateral oophorectomy on ovarian and peritoneal cancers combined. In total, eight case patients with primary peritoneal carcinoma and 128 control subjects reported that they had had a bilateral oo-

Table 1. Characteristics of Israeli women included in the study between 1994 and 1999

Characteristic	Total No. of interviewed subjects		Tested subjects*	
	Case patients (%) N = 1124	Control subjects (%) N = 2396	Case patients (%) N = 847†	Control subjects (%) N = 790
Age, y (range = 21–87)				
<40	48 (4.3)	230 (9.6)	31 (3.7)	68 (8.6)
40–49	208 (18.5)	446 (18.6)	166 (19.6)	138 (17.5)
50–59	263 (23.4)	517 (21.6)	207 (24.4)	166 (21.0)
60–69	329 (29.3)	669 (27.9)	245 (28.9)	238 (30.1)
≥70	276 (24.6)	534 (22.3)	198 (23.4)	180 (22.8)
Ethnic background‡				
Ashkenazi	795 (70.7)	1648 (68.8)	605 (71.4)	548 (69.4)
Non-Ashkenazi	265 (23.6)	584 (24.4)	193 (22.8)	186 (23.5)
Mixed ethnicity	64 (5.7)	164 (6.8)	49 (5.8)	56 (7.1)
History of breast or ovarian cancer in at least one first-degree relative				
None	969 (86.2)	2207 (92.1)	718 (84.8)	721 (91.3)
1 with breast cancer	91 (8.1)	156 (6.5)	72 (8.5)	59 (7.5)
>1 with breast cancer of ≥1 with ovarian cancer	64 (5.7)	33 (1.4)	57 (6.7)	10 (1.3)
Bilateral oophorectomy				
No	1116 (99.3)	2268 (94.7)	840 (99.2)	751 (95.1)
Yes	8 (0.7)	128 (5.3)	7 (0.8)	39 (4.9)
BRCA1/BRCA2 founder mutation status§				
BRCA1 (185delAG or 5382insC)			187 (22.1)	3 (0.4)
BRCA2 (6174delT)			64 (7.6)	10 (1.3)
Either			249 (29.4)	13 (1.6)
Neither			598 (70.6)	777 (98.3)

*BRCA1 and BRCA2 founder mutations were detected as described (9).

†Of the 1124 case patients, 226 did not provide a DNA sample or refused consent to be tested, and 51 DNA samples were of poor quality and no result was obtained.

‡Women born in Europe, North or South America, South Africa, or Israel with two parents from these areas are referred to as Ashkenazi, those born in Israel with one Ashkenazi parent as having mixed ethnicity, and all others as non-Ashkenazi.

§Two case patients tested positive for two of the three founder mutations and were included in both mutation categories.

phorectomy, with the surgery performed from 2 to 24 years earlier. By comparison, 1116 case patients and 2268 control subjects did not report a bilateral oophorectomy; the estimated OR of ovarian or peritoneal cancer among women who had had bilateral oophorectomy was 0.12 (95% CI = 0.06 to 0.24). From the characteristics of the eight case patients (Table 2), there was no distinct pattern in the histology or timing of peritoneal cancer after oophorectomy in BRCA1 mutation carriers.

We next excluded the women with bilateral oophorectomy and examined the association of gynecologic surgeries with some ovarian tissue removal (unilateral oophorectomy, hysterectomy and unilateral oophorectomy, and/or ovarian cystec-

tomy) or without such removal (tubal ligation and hysterectomy with preservation of the ovaries) on ovarian cancer risk (Table 3). Overall, relative to women who did not report any gynecologic surgery, there was an approximately 40% reduction in ovarian cancer risk after any gynecologic surgery (OR = 0.63, 95% CI = 0.50 to 0.79). There was a strong risk reduction in women reporting surgery that involved some removal of ovarian tissue (OR = 0.51, 95% CI = 0.36 to 0.73) relative to women reporting no gynecologic surgery. Women reporting a surgery that did not involve any removal of ovarian tissue also had a reduced ovarian cancer risk (OR = 0.73, 95% CI = 0.55 to 0.96). The association with risk reduction was not limited to

Table 2. Characteristics of the eight women with primary peritoneal carcinoma after bilateral oophorectomy compared with control women reporting bilateral oophorectomy

	Histology	Mutation	Age at bilateral oophorectomy, y	Age at diagnosis/interview, y	No. of years from bilateral oophorectomy to diagnosis/interview
Case patients (n = 8)					
1	Epithelial, unspecified	Not tested	49	67	18
2	Epithelial, adenocarcinoma	Negative	49	73	24
3	Serous, papillary cystadenocarcinoma	Negative	55	60	5
4	Serous, cystadenocarcinoma	BRCA1	47	49	2
5	Epithelial, papillary adenocarcinoma	BRCA1	53	56	3
6	Epithelial, unspecified	BRCA1	44	49	5
7	Serous, cystadenocarcinoma	BRCA1	50	52	2
8	Epithelial, adenocarcinoma	BRCA1	43	49	6
Controls (n = 128)		Not tested (n = 89)	Mean = 51.6 (range = 27–74)	Mean = 62.4 (range = 47–80)	Mean = 10.8 (range = 0–51)
		Negative (n = 39)	Mean = 50.7 (range = 28–73)	Mean = 63.4 (range = 48–78)	Mean = 12.7 (range = 0–39)

Table 3. Association between gynecologic surgeries and ovarian cancer risk among all case patients and all control subjects stratified by type of surgery, ovarian tissue removal, age at procedure, and time since surgery

	All case patients (N = 1124)	All control subjects (N = 2396)	Adjusted* OR (95% CI)
Gynecologic surgery			
No	1002	1929	1.00 (referent)
Yes†	114	339	0.63 (0.50 to 0.79)
Type of surgery‡			
Tubal ligation	20	60	0.70 (0.42 to 1.18)
Oophorectomy and hysterectomy	13	49	0.46 (0.25 to 0.86)
Hysterectomy	57	148	0.69 (0.50 to 0.95)
Unilateral oophorectomy	9	39	0.48 (0.23 to 1.01)
Ovarian cystectomy	24	74	0.61 (0.38 to 0.98)
Ovarian tissue removed			
Yes	41	150	0.51 (0.36 to 0.73)
No	73	189	0.73 (0.55 to 0.96)
Age at surgery, y			
<35	23	84	0.56 (0.35 to 0.90)
35–39	30	56	1.01 (0.64 to 1.60)
40–49	45	125	0.66 (0.46 to 0.94)
≥50	16	72	0.39 (0.22 to 0.68)
Years since surgery			
<5	13	38	0.71 (0.37 to 1.35)
5–9	22	42	1.15 (0.68 to 1.96)
≥10	79	257	0.55 (0.42 to 0.72)

*Adjusted for age, ethnicity, parity, and years of oral contraceptive use. OR = odds ratio; CI = confidence interval.

†Excludes women with bilateral oophorectomy.

‡Some women had more than one surgery and were counted more than once.

||Two women were not included because of missing data on age at surgery and/or years since surgery.

surgeries performed before or after menopause, but was slightly stronger for surgery occurring at or before menopause than for surgery occurring after menopause (data not shown). A statistically significant risk reduction for women reporting a gynecologic surgery was seen only 10 or more years after the reported surgeries (OR = 0.55, 95% CI = 0.42 to 0.72; Table 3).

The associations between gynecologic surgeries and risk of ovarian cancer among the women with known mutation status are shown in Table 4. Five of the eight case patients who reported a bilateral oophorectomy were BRCA1 mutation carriers (OR for ovarian cancer = 0.29, 95% CI = 0.12 to 0.73). Of the other three case patients who had had a bilateral oophorectomy, two were non-carriers, and one refused consent or did not provide a sample. We observed reductions in risk of 66% in BRCA1/2 mutation carriers (OR = 0.34, 95% CI = 0.16 to 0.74) and 61% in non-carriers (OR = 0.39, 95% CI = 0.23 to

0.66), respectively, in women reporting a gynecologic surgery that specifically removed ovarian tissue (unilateral oophorectomy with or without hysterectomy and ovarian cystectomy) relative to those without surgery. We observed a reduction in risk of 33% in BRCA mutation carriers (OR = 0.67, 95% CI = 0.38 to 1.18) and 13% in non-carriers (OR = 0.87, 95% CI = 0.62 to 1.23) from surgeries to the uterus or fallopian tubes that excluded ovarian tissue. Neither reduction was statistically significant. The estimates for associations of individual surgeries were imprecise because of the small numbers of case patients in the subgroups. For example, four carriers and 13 non-carriers had a tubal ligation but no ovarian surgery, and 10 carriers and 34 non-carriers had a hysterectomy but not surgery to the ovaries or fallopian tubes. Women reporting any surgery to the uterus, ovaries, or fallopian tubes had reduced risk relative to those without surgery whether they were carriers (OR = 0.51, 95% CI

Table 4. Association between gynecologic surgeries and the risk of ovarian or peritoneal cancer in tested carriers and non-carriers of BRCA1 and BRCA2 mutations compared with all control subjects

Gynecologic surgery	All control subjects (N = 2396)	Case patients by BRCA1 and BRCA2 mutation status (N = 847)			Adjusted OR (95% CI) for carriers†	Non-carriers (N = 598)	Adjusted OR (95% CI) for non-carriers†
		BRCA1 (N = 187)	BRCA2 (N = 64)	Carriers of both mutations* (N = 249)			
No gynecologic surgery	1929	168	56	223	1.00 (referent)	533	1.0 (referent)
Bilateral oophorectomy	128	5	0	5	0.29 (0.12 to 0.73)	2	0.05 (0.01 to 0.22)
Any gynecologic surgery‡	339	14	8	21	0.51 (0.32 to 0.81)	63	0.66 (0.50 to 0.88)
Surgery with ovarian tissue removed‡,§	150	5	2	7	0.34 (0.16 to 0.74)	16	0.39 (0.23 to 0.66)
Surgery without ovarian tissue removed‡,	189	9	6	14	0.67 (0.38 to 1.18)	47	0.87 (0.62 to 1.23)

*Two carriers were positive for a mutation in both BRCA1 and BRCA2 genes.

†Adjusted for age, ethnicity, parity, and years of oral contraceptive use. OR = odds ratio; CI = confidence interval.

‡Excludes bilateral oophorectomy.

§Includes unilateral oophorectomy with or without hysterectomy and ovarian cystectomy.

||Includes hysterectomy and tubal ligation.

= 0.32 to 0.81) or non-carriers (OR = 0.66, 95% CI = 0.50 to 0.88) of a BRCA mutation.

Among the carriers reporting a gynecologic surgery, the risk of ovarian cancer was 0.46 in BRCA1 mutation carriers (95% CI = 0.26 to 0.80) and 0.72 in BRCA2 mutation carriers (95% CI = 0.34 to 1.5) relative to those reporting no surgery. There was no statistically significant difference in the reduction in risk of ovarian cancer when case patients with BRCA1 mutations were compared directly with case patients with BRCA2 mutations (case-case OR = 0.56, 95% CI = 0.20 to 1.59). The reduction in risk associated with surgery did not vary with the woman's age at diagnosis or with her number of children.

DISCUSSION

Peritoneal cancer, which is histologically indistinguishable from ovarian cancer, can occur in women whose ovaries had been removed prophylactically (17), suggesting that bilateral oophorectomy does not always eliminate risk (18). The risk reduction is critically important to BRCA1 and BRCA2 mutation carriers because of their high risk of developing ovarian cancer. In two clinic-based studies (6,7), women carrying a BRCA mutation who had a prophylactic oophorectomy showed substantially reduced risks of developing ovarian cancer, with hazard ratios of 0.04 (95% CI = 0.01 to 0.16) (7) and 0.15 (95% CI = 0.02 to 1.31) (6). By contrast, we observed an OR of 0.29 (95% CI = 0.12 to 0.73) in the present population-based study of Israeli women. Clearly, ovarian cancer risk is lowered dramatically in BRCA mutation carriers who have undergone bilateral oophorectomy, but more follow-up time and additional studies will be needed to clarify the exact level of risk reduction in carriers within the population.

It is possible that levels of risk reduction depend on the specific location of the mutation. Mutations falling within the so-called "ovarian cancer cluster region" of BRCA2, such as the 6174delT mutation, are associated with an increased risk of ovarian cancer compared with mutations located in other regions of the BRCA2 gene (19). None of the 64 BRCA2 6174delT carrier case patients in this study reported having had a bilateral oophorectomy. Larger numbers of carriers with different BRCA2 mutations must be studied to understand their magnitude of risk reduction following surgery and whether that effect is specific to peritoneal cancers.

We also observed a decreased risk of developing ovarian cancer among BRCA1 and BRCA2 mutation carriers who had other gynecologic surgeries involving the uterus, ovaries, and fallopian tubes. The overall magnitude of the risk reduction we observed in carriers who had previous gynecologic surgery (OR = 0.63, 95% CI = 0.50 to 0.79) was similar to the association seen in non-carriers (OR = 0.66, 95% CI = 0.50 to 0.88) and similar to that seen in a previous prospective study of the risk of ovarian cancer among the general population (12). Our results are also consistent with a report regarding the effects of tubal ligation on ovarian cancer risk in a clinic-based series of prevalent BRCA1 mutation-positive ovarian cancer case patients who were compared with women without ovarian cancer (20).

Among all study participants, we observed that women reporting a bilateral oophorectomy had an almost 90% lower cancer risk. The reduced risk was similar regardless of the age at surgery or whether surgery was performed during or after reproductive years. Similar to a report by Hankinson et al. (12), our study provides evidence that ovarian cancer risk associated

with previous gynecologic surgery persisted beyond 10 years. This long-lasting effect suggests that surveillance alone (i.e., detection that accompanies surgery) could not explain the effect and that risk of developing cancer may actually be lower than that detected.

Our study has several strengths. First, our study uses a well-defined population at risk, namely the population of Israel from 1994 through 1999 with complete ascertainment of case patients, a high response rate, specific, well-defined mutations, the use of incident rather than prevalent case patients, and the availability of extensive data on reproductive and other risk factors. Second, the decisions regarding surgery generally predated the knowledge of BRCA1/2 mutations and were before the routine use of surgery to prevent cancers in carriers. Third, it was possible to evaluate the associations of different types of gynecologic surgery on cancer risk in the Israeli Jewish population—patterns found to be typical of those reported in many population studies. It was also possible to compare patterns in the subset of women who carried BRCA1/2 mutations with patterns in women who did not. Our analysis did not rely on the very small number of carrier controls we identified. Comparing the patterns of multiple surgical associations between carriers and non-carriers provides a broader base of evidence to detect whether surgical intervention operates similarly in carriers and non-carriers.

Our study has several limitations. First, unlike a prospective clinical cohort study, our study relies on self-reports of surgery and routine classification of the primary origin of the tumor as ovary, tubal, or peritoneal. In a woman with both ovarian and peritoneal involvement, the likelihood of assigning the peritoneum as the primary site is influenced by the presence of ovaries. In our large population series, 80 peritoneal cancers were noted in women who had ovaries. Second, even in this large study, the number of women with a specific mutation was not large, so the confidence intervals are wide. For example, only two of the BRCA2 mutation carriers in this study had had a tubal ligation. Third, women in our study may harbor a non-founder mutation. Because non-founder mutations seldom occur in Ashkenazi women (21), we repeated the analysis with restriction to Ashkenazi participants. We found no substantial difference in the risk estimates (data not shown). Finally, like our earlier report (9), this analysis relies on an unverified assumption regarding independence between genetic and behavioral factors, conditional on family history of cancer. We note that the confidence intervals we report are still too narrow because they do not take remaining uncertainty about this assumption into account (14).

Although the relation between gynecologic surgery and reduced risk of ovarian cancer in general is well established (22–25), the underlying mechanisms are not completely clear. Gynecologic surgeries such as tubal ligation, hysterectomy, and/or unilateral oophorectomy may reduce the risk of ovarian cancer by reducing the number of ovulations. Studies in the 1970s and 1980s suggested that menstrual disorders, including reduced ovulation and accelerated onset of menopause, often occurred after tubal ligation, which may have been a direct result of a reduced blood supply to the ovaries (26–29) and lower gonadotropin levels that act by stimulating the ovarian surface epithelium (30). This proposed mechanism applies directly to hysterectomy and unilateral oophorectomy, but it is unclear whether current tubal ligation procedures would substantially decrease

blood flow to the ovaries. An alternative mechanism could be that tubal ligation procedures occlude the fallopian tube, thereby blocking passage of potential environmental carcinogens (e.g., talc) to the ovary, where they would otherwise induce an inflammatory response and subsequent malignant transformation (31).

Various investigations have assessed whether the lower ovarian cancer risk seen following gynecologic surgery reflects screening that accompanies the surgery. For instance, women may have been found unexpectedly to have ovarian cancer at the time of tubal ligation or hysterectomy surgery, or some may have had abnormal ovaries removed that may have otherwise become malignant. The published data do not, however, support such a screening hypothesis. For example, one prospective study (12) found that the reduced risk associated with hysterectomy persisted at least 15 years after the procedure (relative risk = 0.62, 95% CI = 0.31 to 1.22); another (25) showed persistently reduced risk 30 years after surgery. Both reports (12,25) suggest that the risk reduction is unlikely to be the result of a screening effect alone.

Few non-surgical options to reduce ovarian cancer risk are available to high-risk women. Routine screening with ultrasound and antibody tests have not yet been shown to be effective. Oral contraceptive use was reported to be associated with reduced risk in a clinic-based series of BRCA mutation carriers (32), but this finding was not confirmed in our population-based case-control study (9). Thus, tubal ligation, hysterectomy, and/or unilateral oophorectomy may be options for BRCA mutation carriers who seek a means of reducing their risk of ovarian cancer. This option may be desirable to genetically at-risk women who have completed childbearing but who want to avoid complete bilateral oophorectomy and the possible morbidities associated with it. For example, premenopausal women may want to reduce their need for hormone replacement therapy. These are complicated decisions, in part because women who carry a germline mutation in BRCA1/2 have an increased risk not only of ovarian cancer but also of breast cancer. Regardless, prophylactic oophorectomy is an option for at-risk women despite the possibility of subsequent occurrence of primary peritoneal cancers.

Gynecologic surgeries may offer some reduction in risk of breast cancer. Tubal ligation does not seem to reduce breast cancer risk, but other gynecologic procedures, such as hysterectomy, unilateral oophorectomy, and bilateral oophorectomy do (33,34). The reduction in breast cancer risk may be related to the altered exposure to endogenous ovarian hormones following hysterectomy and oophorectomy. Furthermore, long-term hormone replacement therapy may increase risk of breast cancer (35), although at least one recent report found that BRCA1 mutation carriers who had a prophylactic oophorectomy showed no increased breast cancer risk with hormone replacement therapy use (36).

Taken together, the current evidence suggests that gynecologic surgeries can reduce risk of ovarian cancer in carriers of BRCA1/2 mutations. Bilateral oophorectomy may remove most of the risk, other surgeries that remove ovarian tissue may halve the risk, and hysterectomy and tubal ligation may modestly reduce the risk. Clinical decisions for ovarian cancer risk reduction in BRCA mutation carriers will necessarily involve the balancing of potential benefits and harms for each individual woman faced with this difficult decision.

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NOTES

¹*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit orga-

nizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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