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RISK-REDUCING SALPINGO-OOPHORECTOMY IN WOMEN WITH A *BRCA1* OR *BRCA2* MUTATION

NOAH D. KAUFF, M.D., JAYA M. SATAGOPAN, PH.D., MARK E. ROBSON, M.D., LAUREN SCHEUER, M.S.,
MARTEE HENSLEY, M.D., CLIFFORD A. HUDIS, M.D., NATHAN A. ELLIS, PH.D., JEFF BOYD, PH.D., PATRICK I. BORGEN, M.D.,
RICHARD R. BARAKAT, M.D., LARRY NORTON, M.D., AND KENNETH OFFIT, M.D., M.P.H.

ABSTRACT

Background Risk-reducing salpingo-oophorectomy is often considered by carriers of *BRCA* mutations who have completed childbearing. However, there are limited data supporting the efficacy of this approach. We prospectively compared the effect of risk-reducing salpingo-oophorectomy with that of surveillance for ovarian cancer on the incidence of subsequent breast cancer and *BRCA*-related gynecologic cancers in women with *BRCA* mutations.

Methods All women with *BRCA1* or *BRCA2* mutations identified during a six-year period were offered enrollment in a prospective follow-up study. A total of 170 women 35 years of age or older who had not undergone bilateral oophorectomy chose to undergo either surveillance for ovarian cancer or risk-reducing salpingo-oophorectomy. Follow-up involved an annual questionnaire, telephone contact, and reviews of medical records. The time to cancer in the two groups was compared by Kaplan–Meier analysis and a Cox proportional-hazards model.

Results During a mean follow-up of 24.2 months, breast cancer was diagnosed in 3 of the 98 women who chose risk-reducing salpingo-oophorectomy and peritoneal cancer was diagnosed in 1 woman in this group. Among the 72 women who chose surveillance, breast cancer was diagnosed in 8, ovarian cancer in 4, and peritoneal cancer in 1. The time to breast cancer or *BRCA*-related gynecologic cancer was longer in the salpingo-oophorectomy group, with a hazard ratio for subsequent breast cancer or *BRCA*-related gynecologic cancer of 0.25 (95 percent confidence interval, 0.08 to 0.74).

Conclusions Salpingo-oophorectomy in carriers of *BRCA* mutations can decrease the risk of breast cancer and *BRCA*-related gynecologic cancer. (N Engl J Med 2002;346:1609-15.)

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WOMEN with *BRCA1* or *BRCA2* mutations have a 60 to 85 percent cumulative lifetime risk (to 70 years of age) of invasive breast cancer and a 15 to 65 percent cumulative lifetime risk of invasive epithelial ovarian cancer.¹⁻³ Because of a paucity of prospective data regarding the efficacy of preventive approaches in carriers of *BRCA* mutations, counseling about screening, chemoprevention, and risk-reducing surgery has been based largely on expert opinion.⁴ We have previously found that a combination of intense surveillance and risk-reducing surgery in carriers of *BRCA* mutations may allow the diagnosis of breast and ovarian cancers at an early stage.⁵ Recent data also suggest that prophylactic mastectomy reduces the risk of breast cancer.⁶

Salpingo-oophorectomy for the prevention of ovarian and fallopian-tube cancers in carriers of *BRCA1* and *BRCA2* mutations is widely recommended,^{4,7} but support for this approach comes from retrospective studies in which participants either were not genotyped⁸ or were in some cases included in the analysis after self-selection for genetic testing years after the preventive surgery.⁹ Reports of primary peritoneal cancer after oophorectomy in women at risk for hereditary ovarian cancer have called into question the ef-

From the Clinical Genetics Service (N.D.K., M.E.R., L.S., N.A.E., J.B., K.O.), the Breast Cancer Medicine Service (M.E.R., C.A.H., L.N.), and the Developmental Chemotherapy Service (M.H.), Department of Medicine; the Department of Epidemiology and Biostatistics (J.M.S.); and the Gynecology Service (J.B., R.R.B.) and the Breast Service (P.I.B.), Department of Surgery — all at Memorial Sloan-Kettering Cancer Center, New York. Address reprint requests to Dr. Offit at the Clinical Genetics Service, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021, or at offitk@mskcc.org.

Other authors were Mercedes Castiel, M.D. (Gynecology Service, Department of Surgery), and Khedoudja Nafa, Ph.D. (Clinical Genetics Service, Department of Medicine), Memorial Sloan-Kettering Cancer Center, New York.

ficacy of this procedure for the prevention of *BRCA*-related gynecologic (ovarian, fallopian-tube, and primary peritoneal) cancers.¹⁰⁻¹³ Retrospective series have also suggested that oophorectomy may protect against hereditary breast cancers.¹⁴ We report a prospective evaluation of the role of salpingo-oophorectomy in reducing the risk of breast cancer and *BRCA*-related gynecologic cancers in carriers of *BRCA1* and *BRCA2* mutations.

METHODS

Study Subjects

All women evaluated for possible pathogenic *BRCA1* or *BRCA2* mutations in the context of genetic counseling at Memorial Sloan-Kettering Cancer Center in New York between June 1, 1995, and May 30, 2001, were offered enrollment in one of three follow-up studies that had been approved by the institutional review board. The study protocols and the results of a different analysis have been described in a previous report.⁵ The current analysis contains additional follow-up and clinical information on 154 patients included in that report, as well as data on 23 carriers of *BRCA* mutations who were not included in that study. In the current study, we analyzed the prevention of cancer (the reduction in incidence) with surgery as compared with surveillance, whereas the previous study was limited to an analysis of the stage of the cancers that were detected.

Of 272 women found to carry a pathogenic *BRCA1* or *BRCA2* mutation, 265 elected to participate in follow-up studies. Of these 265 women, 63 who had undergone bilateral salpingo-oophorectomy before genetic testing were excluded from the analysis. An additional 25 women who were younger than 35 years of age at the time of testing were also excluded because, in our study, carriers of *BRCA* mutations were advised to initiate screening for ovarian cancer or consider risk-reducing oophorectomy after 35 years of age.

All remaining 177 women from 153 families were advised by physicians and staff of the Clinical Genetic Service of the hospital to begin surveillance for ovarian cancer with annual or twice-yearly gynecologic examinations, twice-yearly transvaginal ultrasonographic examinations, and twice-yearly determinations of the serum CA-125 concentration. For women whose childbearing was complete, consideration of salpingo-oophorectomy was recommended. All women with breast tissue at risk (i.e., who had not had bilateral mastectomies) were advised to undergo annual mammographic examinations, to have clinical breast examinations two to four times per year, and to perform breast self-examinations monthly. The option of risk-reducing mastectomy was also discussed. Patients chose their own screening and preventive interventions.

Follow-up through November 30, 2001, involved an annual questionnaire, telephone contact, and review of medical records. Pathology reports were obtained for all new cancers diagnosed during follow-up. Pathology reports were also obtained for 92 percent of risk-reducing surgical procedures. Four patients who were lost to follow-up before the first follow-up contact were excluded from the analysis. Three patients were found to have unsuspected early-stage gynecologic cancer (two had ovarian cancer, and one had fallopian-tube cancer) at the time of risk-reducing salpingo-oophorectomy and were excluded from the statistical analysis of cancer end points.

Statistical Analysis

The salpingo-oophorectomy group included all women who had a risk-reducing salpingo-oophorectomy with or without concomitant hysterectomy after the receipt of genetic-test results. The surveillance group included all women who did not elect to undergo risk-reducing salpingo-oophorectomy. Women who had a therapeutic

oophorectomy because of abnormalities found through surveillance for ovarian cancer were included in the surveillance group, and their follow-up data were censored at the date of oophorectomy. For women in the surveillance group, the duration of follow-up was calculated from the date of receipt of genetic-test results to the date of diagnosis of new breast or *BRCA*-related gynecologic cancer, the date of last contact, or the date of death. For women in the salpingo-oophorectomy group, the duration of follow-up was calculated from the date of salpingo-oophorectomy to the date of diagnosis of new breast or *BRCA*-related gynecologic cancer, the date of last contact, or the date of death.

The demographic characteristics of the two groups were compared with the use of the independent-sample t-test for continuous variables and Fisher's exact test for discrete variables. Kaplan-Meier analysis and the log-rank test were used to compare the two groups in terms of the time to a subsequent diagnosis of cancer.

To calculate the hazard ratio for the combined incidence of breast cancer and *BRCA*-related gynecologic cancer after risk-reducing salpingo-oophorectomy, we used a Cox proportional-hazards model for multiple events.^{15,16} This model allowed us to adjust for both differing frequency and differing timing of bilateral mastectomy between the two groups by censoring follow-up data related to breast cancer at the time of bilateral mastectomy. A Cox proportional-hazards model was also used to determine the separate hazard ratios for breast cancer after risk-reducing salpingo-oophorectomy and for *BRCA*-related gynecologic cancer after such surgery. Analyses were performed with the use of SPSS software (version 10.0, SPSS) and S-Plus software (version 6, Insightful). All reported P values are two-sided.

RESULTS

Of 170 women who met the criteria for entry, 98 elected to undergo risk-reducing salpingo-oophorectomy a median of 3.6 months after receiving the results of genetic testing, and 72 chose surveillance for ovarian cancer. There was no significant difference between the two groups in terms of mean age, percentage with *BRCA1* or *BRCA2* mutations, mean number of first- and second-degree relatives with breast, ovarian, fallopian-tube, or primary peritoneal cancer, and percentage with a history of breast cancer, systemic chemotherapy, or oral-contraceptive use. More women in the salpingo-oophorectomy group than in the surveillance group (29 of 98 women [30 percent] vs. 10 of 72 women [14 percent]) had undergone bilateral mastectomy before the start of follow-up ($P=0.02$). There was no significant difference in the number of women who underwent bilateral mastectomy during a mean of 24.2 months of follow-up. Complete demographic information for the two groups is summarized in Table 1.

Time to Cancer

Total follow-up was 191 woman-years in the salpingo-oophorectomy group and 152 woman-years in the surveillance group. When follow-up data were censored at the time of diagnosis of ovarian cancer or therapeutic oophorectomy, there were 139 woman-years of follow-up for the 72 women who elected surveillance for ovarian cancer. Ovarian cancer was diagnosed in four women and primary peritoneal cancer in one woman a mean of 17.0 months after the

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF THE WOMEN.

CHARACTERISTIC	SALPINGO-OOPHORECTOMY GROUP (N=98)	SURVEILLANCE GROUP (N=72)	P VALUE*
Age at the time of genetic test — yr			0.17
Mean	47.5	45.5	
Median	45.5	42.4	
Range	35.9–73.9	35.0–77.7	
Type of mutation — no. (%)			0.27
<i>BRCA1</i>	56 (57)	48 (67)	
<i>BRCA2</i>	42 (43)	24 (33)	
No. of first- or second-degree relatives with breast, ovarian, fallopian-tube, or primary peritoneal cancer			0.20
Mean	1.64	1.86	
Range	0–4	0–5	
Previous breast cancer — no. (%)	69 (70)	45 (62)	0.32
Age at the time of first breast cancer — yr			0.21
Mean	41.6	39.7	
Range	25–70	26–68	
Previous chemotherapy — no. (%)	60 (61)	39 (54)	0.43
Bilateral mastectomy — no. (%)			
Previous	29 (30)	10 (14)	0.02
During follow-up	9 (9)	6 (8)	1.00
Previous oral-contraceptive use — no./no. with data (%)	61/91 (67)	40/61 (66)	0.86
Duration of surveillance before risk-reducing salpingo-oophorectomy — mo			
Median	3.6	—	
Range	0.2–63.3	—	
Duration of follow-up after risk-reducing salpingo-oophorectomy or start of surveillance — mo			0.48
Mean	23.4	25.4	
Median	20.0	20.4	
Range	0.1–71.7	0.4–76.2	
No. of woman-years of follow-up	191	152	

*P values were calculated with the use of Fisher's exact test for discrete variables and the independent-sample t-test for continuous variables.

receipt of genetic-test results. All these cancers were diagnosed after suspicious or persistent abnormalities were noted either on transvaginal ultrasonography or in the serum CA-125 concentration. An additional seven women in the surveillance group had suspicious or persistent abnormalities that prompted surgical exploration a mean of 1.8 months after the receipt of genetic-test results. In all seven cases, the findings represented benign conditions. With a mean follow-up of 15.3 months after surgery, no new breast or gynecologic cancers had been diagnosed in these seven women.

During 191 woman-years of follow-up in the 98 women who chose to undergo salpingo-oophorectomy, primary peritoneal cancer was diagnosed in 1 woman 16.3 months after salpingo-oophorectomy. No other woman in this group underwent surgical exploration after salpingo-oophorectomy.

During 120 woman-years of follow-up in the 62

women with breast tissue in the surveillance group, breast cancer was diagnosed in 8 women a mean of 12.7 months after the receipt of genetic-test results. During 127 woman-years of follow-up in the 69 women with breast tissue in the salpingo-oophorectomy group, breast cancer was diagnosed in 3 women a mean of 10.3 months after risk-reducing salpingo-oophorectomy.

When the two types of cancer were analyzed together, breast cancer or *BRCA*-related gynecologic cancer was found to have been diagnosed in a total of four women in the salpingo-oophorectomy group during 186 woman-years of follow-up. In the surveillance group, 13 such cancers were diagnosed in 12 women during 135 woman-years of follow-up (Fig. 1). The estimated proportion free from breast cancer or *BRCA*-related gynecologic cancer at five years (according to the Kaplan–Meier analysis) was significantly greater in the salpingo-oophorectomy group ($P=$

0.006) (Table 2). To take into account the different proportions of women in the two groups who had undergone bilateral mastectomy before study entry, a Cox proportional-hazards model for multiple events was used. This analysis revealed that the hazard ratio for the development of breast cancer or *BRCA*-related gynecologic cancer after risk-reducing salpingo-oophorectomy was 0.25 (95 percent confidence interval, 0.08 to 0.74) (Table 3). There was no significant effect of the type of mutation (*BRCA1* vs. *BRCA2*) on the time to breast or gynecologic cancer ($P=0.31$).

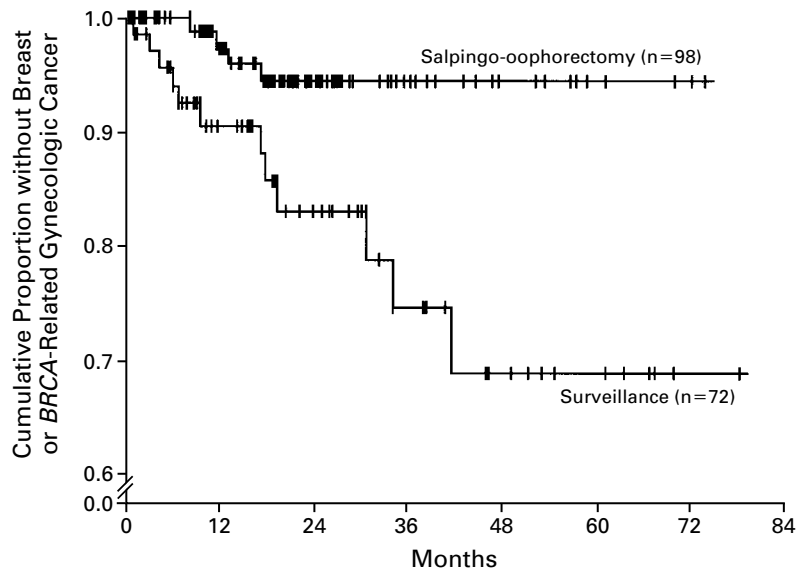
When the analysis was limited to new ovarian, fallopian-tube, and primary peritoneal cancers, the time to a diagnosis of cancer was longer in the salpingo-oophorectomy group than in the surveillance group ($P=0.04$) (Table 2). The hazard ratios for the development of *BRCA*-related gynecologic cancer or breast cancer after salpingo-oophorectomy are shown in Table 3.

Among the women in the surveillance group for whom detailed data were available, 51 of 63 (81 percent) indicated that they were undergoing ultrason-

ographic surveillance, CA-125-based surveillance, or both. Among patients undergoing such surveillance for ovarian cancer, a mean of 1.73 transvaginal ultrasonographic examinations (range, 1 to 4) and 1.68 determinations of the serum CA-125 concentration (range, 1 to 4) per year were reported. A total of 51 of 58 women with breast tissue in this group (88 percent) also underwent regular mammographic examination. In the salpingo-oophorectomy group, 63 of 65 women with breast tissue for whom data were available (97 percent) underwent regular mammographic examination. The risk of breast cancer or *BRCA*-related gynecologic cancer was significantly lower among the 98 women in the salpingo-oophorectomy group than among the 51 women who indicated that they were undergoing ultrasonographic surveillance, CA-125-based surveillance, or both (hazard ratio, 0.19; 95 percent confidence interval, 0.06 to 0.56).

Complications of Risk-Reducing Salpingo-oophorectomy

Complications were noted in 4 of the 80 women who underwent risk-reducing salpingo-oophorectomy



NO. AT RISK	0	12	24	36	48	60	72	84
Salpingo-oophorectomy	98	69	36	17	11	4	0	
Surveillance	72	44	28	16	9	5	1	

Figure 1. Kaplan–Meier Estimates of the Time to Breast Cancer or *BRCA*-Related Gynecologic Cancer among Women Electing Risk-Reducing Salpingo-oophorectomy and Women Electing Surveillance for Ovarian Cancer.

$P=0.006$ by the log-rank test for the comparison between the actuarial mean times to cancer. A Cox proportional-hazards model for multiple end points, which took into account the different proportions of women in the two groups who had breast tissue at risk, yielded a hazard ratio for subsequent breast cancer or *BRCA*-related gynecologic cancer after risk-reducing salpingo-oophorectomy of 0.25 (95 percent confidence interval, 0.08 to 0.74).

TABLE 2. KAPLAN–MEIER ESTIMATES OF PROPORTIONS FREE FROM CANCER.

VARIABLE	SALPINGO-OOPHORECTOMY GROUP (N=98)	SURVEILLANCE GROUP (N=72)	P VALUE*
Ovarian, fallopian-tube, or primary peritoneal cancer			0.04
No.	1	5	
Projected proportion free from cancer at 5 yr (%)	98	83	
Breast cancer†			0.07
No.	3	8	
Projected proportion free from cancer at 5 yr (%)	94	79	
Breast cancer or <i>BRCA</i> -related gynecologic cancer			0.006
No.	4	12‡	
Projected proportion free from cancer at 5 yr (%)	94	69	

*P values were determined by the log-rank test.

†The Kaplan–Meier analysis was limited to the 131 women with breast tissue at the start of follow-up.

‡Metachronous breast and ovarian cancers were diagnosed in one patient in this group during follow-up.

TABLE 3. HAZARD OF BREAST CANCER OR *BRCA*-RELATED GYNECOLOGIC CANCER AFTER RISK-REDUCING SALPINGO-OOPHORECTOMY.*

VARIABLE	OVARIAN, FALLOPIAN-TUBE, OR PRIMARY PERITONEAL CANCER	BREAST CANCER	BREAST CANCER OR <i>BRCA</i> -RELATED GYNECOLOGIC CANCER
No. of patients included in analysis	170	131	170
Mean no. of months of follow-up	23.3	22.6	22.7
Hazard ratio (95% CI)	0.15 (0.02–1.31)	0.32 (0.08–1.20)	0.25 (0.08–0.74)

*Hazard ratios were calculated with the Cox proportional-hazards model for multiple events, and follow-up data related to breast cancer were censored at the time of bilateral mastectomy. CI denotes confidence interval.

without hysterectomy. In one woman, a laparoscopic salpingo-oophorectomy was converted to a laparotomy because there were multiple adhesions at the site of a previous repair of an umbilical hernia. Her postoperative course was complicated by an infection of the wound. In a second woman who underwent laparoscopic salpingo-oophorectomy, perforation of the bladder during the placement of a trocar necessitated drainage by a Foley catheter for five days. A third woman presented with a distal obstruction of the small bowel eight weeks after risk-reducing salpingo-oophorectomy. Operative findings were nota-

ble for adhesions between the distal ileum and staples on the right ovarian vessels, which caused a small-bowel obstruction at that point. The obstruction was relieved by lysis of the adhesions without need for bowel resection. In a fourth woman who underwent laparoscopic salpingo-oophorectomy, perforation of the uterus by a uterine manipulator necessitated laparoscopic suturing of the uterus and overnight observation. No complications were noted in 11 women who had a hysterectomy at the time of risk-reducing salpingo-oophorectomy or in 7 women whose uterine-surgery status at the time of risk-reducing salpingo-oophorectomy was not specified.

DISCUSSION

In this study, we prospectively evaluated 170 women with germ-line *BRCA* mutations who elected either risk-reducing salpingo-oophorectomy or surveillance for ovarian cancer. Survival free of breast cancer and *BRCA*-related gynecologic cancer was longer in the cohort that chose salpingo-oophorectomy: the projected proportion of women who will be free of breast cancer or *BRCA*-related gynecologic cancer five years from the time of salpingo-oophorectomy or the beginning of surveillance is 94 percent in the salpingo-oophorectomy group and 69 percent in the surveillance group. Three patients who were not included in the actuarial analysis were found to harbor an occult stage I gynecologic neoplasm at the time of what had been considered to be risk-reducing surgery. Taken together, these results provide strong support for including discussion of risk-reducing salpingo-oophorectomy as part of a preventive-oncology strat-

egy for women with a *BRCA1* or *BRCA2* mutation. Our findings recall those of Meijers-Heijboer et al.,⁶ who showed in a similar prospective study that risk-reducing mastectomy decreased the risk of breast cancer in carriers of *BRCA* mutations.

The protective effect of salpingo-oophorectomy in this series was slightly lower than that found in a recent retrospective analysis.⁹ The greater effect in that study may have reflected underascertainment of peritoneal cancers in carriers of *BRCA* mutations who had previously undergone oophorectomy. The trend toward a decreased risk of breast cancer after oophorectomy in our series is consistent with a previous retrospective case-control series¹⁴ and with the finding that hormone deprivation has a beneficial effect on the risk of breast cancer.¹⁷⁻²⁰ The moderate reduction we found in the incidence of breast cancer must, however, be compared with the results recently documented by Meijers-Heijboer et al., in whose study no case of breast cancer occurred after prophylactic mastectomy in 76 women with *BRCA* mutations followed for the same length of time as in our series.⁶

The incidence of breast cancer and *BRCA*-related gynecologic cancer in our study of 53 cases per 1000 woman-years is somewhat higher than the 21 to 42 cases per 1000 woman-years that would be predicted on the basis of linkage studies.²¹⁻²³ This higher incidence may reflect the presence of preexisting cancers that were detected during the first year of follow-up. When the eight patients in whom cancer was diagnosed during the first year of follow-up are excluded from the analysis, the incidence of cancer in our cohort is 25 per 1000 woman-years, which falls within the range derived from linkage studies.

Only 4 of 98 risk-reducing salpingo-oophorectomy procedures (4 percent) in this series were associated with surgical complications. This rate is similar to those reported in other studies of laparoscopic gynecologic procedures^{24,25} and lower than the complication rate of 8 to 17 percent associated with abdominal hysterectomy and concomitant bilateral salpingo-oophorectomy.^{26,27} This rate contrasts with the complication rate of up to 30 percent that has been reported for risk-reducing mastectomy with reconstruction.²⁸

Approximately 12 percent of the risk-reducing salpingo-oophorectomy procedures in our series included removal of the uterus. Although there is no proven increase in the risk of uterine cancer in carriers of *BRCA* mutations,²⁹ several authors have recommended concomitant hysterectomy because of the risk of cancer arising from the small amount of intramural fallopian-tube tissue that is left by salpingo-oophorectomy.^{30,31} In a previous series, five cases of peritoneal carcinomatosis occurred after hysterectomy with bilateral oophorectomy in women with a hereditary predisposition to cancer.¹¹ Whether hysterectomy fur-

ther reduces the risk of cancer is unknown, and prospective studies will be required in order to resolve this question.

Although the median time between genetic testing and risk-reducing salpingo-oophorectomy was only 3.6 months, a possible bias may have been introduced by beginning follow-up in the salpingo-oophorectomy group at the time of surgery. According to an analysis in which follow-up for all patients began at the time of notification of genetic-test results, however, salpingo-oophorectomy remained highly protective against breast cancer and *BRCA*-related gynecologic cancer (hazard ratio, 0.21; 95 percent confidence interval, 0.07 to 0.62). If the three cases of unsuspected gynecologic cancer detected at the time of risk-reducing surgery were included in this analysis, the hazard ratio for development of breast or *BRCA*-related gynecologic cancer would be 0.37 (95 percent confidence interval, 0.12 to 0.90). Another limitation of our study was the selection of time to cancer rather than overall survival as an end point. Salpingo-oophorectomy may have adverse effects on the lipid profile³² and may increase the risks of cardiovascular disease³³ and osteoporosis.³⁴ There may also be psychosocial and sexual effects. A recent study demonstrated that women who underwent this type of surgery had more physical and emotional symptoms than those who underwent screening.³⁵

Whether our results will translate into improved survival will depend, in large part, on the effectiveness of screening for ovarian cancer. We have found early-stage gynecologic cancers with ovarian ultrasonography and CA-125-based screening,⁵ but these screening methods can fail to detect ovarian cancers at a curable stage.³⁶⁻³⁹ Hormonal chemoprevention of breast cancer and ovarian cancer offers an additional potential strategy for some carriers of *BRCA* mutations.^{40,41} In the absence of novel imaging techniques or new serum markers that can predictably identify early-stage ovarian and fallopian-tube neoplasms, risk-reducing salpingo-oophorectomy remains an important option for women at risk for hereditary breast or gynecologic cancer.

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