Title

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Journal

JAMA Oncology, 2(11)

ISSN

2374-2437

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Publication Date

2016-11-01

DOI

10.1001/jamaoncol.2016.1820

Peer reviewed

Published in final edited form as:

JAMA Oncol. 2016 November 01; 2(11): 1434–1440. doi:10.1001/jamaoncol.2016.1820.

Uterine cancer after risk-reducing salpingo-oophorectomy without hysterectomy in women with *BRCA* mutations

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Conflict of Interest Disclosures: Dr. Soslow receives royalties from Cambridge University Press and Springer, and has served as a consultant to EMD Serono, Inc. No other conflicts were reported.

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Abstract

Importance—The link between *BRCA* mutations and uterine cancer is unclear. Therefore, although risk-reducing salpingo-oophorectomy (RRSO) is standard treatment among women with *BRCA* mutations (*BRCA*+ women), the role of concomitant hysterectomy is controversial.

Objective—To determine the risk for uterine cancer and distribution of specific histologic subtypes in *BRCA*+ women after RRSO without hysterectomy.

Design, Setting, and Participants—This multicenter prospective cohort study included 1083 women with a deleterious *BRCA1* or *BRCA2* mutation identified from January 1, 1995, to December 31, 2011, at 9 academic medical centers in the United States and the United Kingdom who underwent RRSO without a prior or concomitant hysterectomy. Of these, 627 participants were *BRCA1*+; 453, *BRCA2*+; and 3, both. Participants were prospectively followed up for a median 5.1 (interquartile range [IQR], 3.0–8.4) years after ascertainment, *BRCA* testing, or RRSO (whichever occurred last). Follow up data available through October 14, 2014, were included in the analyses. Censoring occurred at uterine cancer diagnosis, hysterectomy, last follow-up, or death. New cancers were categorized by histologic subtype, and available tumors were analyzed for loss of the wild-type *BRCA* gene and/or protein expression.

Main Outcomes and Measures—Incidence of uterine corpus cancer in *BRCA*+ women who underwent RRSO without hysterectomy compared with rates expected from the Surveillance, Epidemiology, and End Results database.

Results—Among the 1083 women women who underwent RRSO without hysterectomy at a median age 45.6 (IQR: 40.9 – 52.5), 8 incident uterine cancers were observed (4.3 expected; observed to expected [O:E] ratio, 1.9; 95% CI, 0.8–3.7; $P = .09$). No increased risk for endometrioid endometrial carcinoma or sarcoma was found after stratifying by subtype. Five serous and/or serous-like (serous/serous-like) endometrial carcinomas were observed (4 *BRCA1*+ and 1 *BRCA2*+) 7.2 to 12.9 years after RRSO (*BRCA1*: 0.18 expected [O:E ratio, 22.2; 95% CI, 6.1–56.9; $P < .001$]; *BRCA2*: 0.16 expected [O:E ratio, 6.4; 95% CI, 0.2–35.5; $P = .15$]). Tumor analyses confirmed loss of the wild-type *BRCA1* gene and/or protein expression in all 3 available serous/serous-like *BRCA1*+ tumors.

Conclusions and Relevance—Although the overall risk for uterine cancer after RRSO was not increased, the risk for serous/serous-like endometrial carcinoma was increased in *BRCA1*+ women. This risk should be considered when discussing the advantages and risks of hysterectomy at the time of RRSO in *BRCA1*+ women.

Introduction

In 2002, Kauff et al[1] and Rebbeck et al[2] published the first 2 studies demonstrating that risk-reducing salpingo-oophorectomy (RRSO) decreased the risk for breast and ovarian or fallopian tube cancer in women with mutations in the *BRCA1* (OMIM 113705) (*BRCA1*+ women) or *BRCA2* (OMIM 600185) (*BRCA2*+ women) gene. Subsequent studies have confirmed that RRSO not only reduces the risk for ovarian or fallopian tube cancer by 80% to 90% and the risk for breast cancer by 40% to 70%[3–5] but also reduces disease-specific and overall mortality.[4,5]

Although RRSO is now part of standard management for *BRCA*+ women, the role of concomitant hysterectomy remains controversial.[6,7] Some studies[8,9] have suggested that *BRCA*+ women may be at higher risk for uterine corpus cancer, while others[10] have suggested that the risk is predominantly associated with tamoxifen citrate use. Further reports[11,12] have suggested that more aggressive, serous and/or serous-like (serous/serous-like) endometrial carcinoma is overrepresented in *BRCA*+ women, but other studies[13,14] have not confirmed this. Clarification of this issue is particularly relevant, because the serous/serous-like subtype accounts for only about 10% of uterine corpus cancer cases but more than 40% of deaths due to the disease.[15]

To provide data relevant to these questions, we conducted a multicenter, prospective evaluation of uterine corpus cancer risk after RRSO in *BRCA1*+ and *BRCA2*+ women. We also examined whether specific histologic subtypes were overrepresented.

METHODS

Study Participants

Women were eligible for this study if they (1) had a deleterious *BRCA* mutation identified from January 1, 1995, to December 31, 2011; (2) underwent RRSO with their uterus left in situ; (3) did not have ovarian, fallopian tube, or uterine cancer before the later of genetic testing or RRSO; and (4) consented in writing to participation in one of several institutional review board–approved prospective follow-up studies conducted at the University of Pennsylvania, Memorial Sloan Kettering Cancer Center, and 7 academic centers participating in the Prevention and Observation of Surgical End Points Study (PROSE Consortium), including Baylor–Charles A. Sammons Cancer Center, City of Hope Medical Center, Dana-Farber Cancer Institute, Fox Chase Cancer Center, Lombardi Cancer Center, Royal Marsden Hospital, and UCLA Jonsson Comprehensive Cancer Center.

Women were followed up via structured questionnaire and medical record review as previously described.[1–3,16] Information regarding risk-reducing and therapeutic surgical procedures, medication exposures, and new malignant neoplasms was ascertained.

Pathology reports were requested for all new uterine corpus cancers diagnosed during follow-up. No individuals were excluded owing to race or ethnicity. Race or ethnicity designations were self-reported and collected to assist in determining expected age- and race-specific cancer incidence.

Statistical Analysis

Follow-up time began from the latest of date of ascertainment, receipt of *BRCA* testing results, or RRSO. The main outcome of interest was the diagnosis of uterine cancer. Censoring events were hysterectomy, last follow-up, or death. Women were considered to be at risk from 30 years and older, and women with less than 6 months of follow-up were excluded. Follow-up data available through October 14, 2014, were included in the analyses.

Expected incidence of uterine cancer was calculated by multiplying woman-years at risk by the age- and race-specific data from the Surveillance, Epidemiology, and End Results database (SEER*Stat database: Incidence—SEER 18 registries, November 2012 [submitted 2000–2010]), categorized by age into 5-year increments.[17] Because 31% of US women have undergone hysterectomy by 60 years of age, expected incidences were adjusted for the age- and race-specific prevalence of hysterectomy, obtained using the 2010 Cross Tabulation Analysis Tool from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System (BRFSS),[18] and grouped in 5-year increments of age as indicated in the following equation:

$$\text{Adjusted Incidence} = \text{SEER Expected Incidence} / (1 - \text{BRFSS Hysterectomy Prevalence}).$$

To determine the expected incidence of specific histologic subtypes, we used codes from the *International Classification of Diseases for Oncology* (*ICD-O*) to assign SEER cases into 1 of the following 5 histologic categories: (1) endometrioid endometrial carcinoma (eg, endometrioid, adenocarcinoma not otherwise specified); (2) serous/serous-like endometrial carcinoma (eg, serous, undifferentiated, carcinosarcoma); (3) clear cell carcinoma; (4) mucinous carcinoma; and (5) uterine sarcoma. Specific *ICD-O* codes assigned to each category are detailed in eTable 1 in the Supplement. Carcinosarcomas, which are epithelial cancers rather than sarcomas, were included in the serous/serous-like category, because these are frequently thought to have dedifferentiated from a serous precursor, and the carcinomatous component is the primary driver of tumor aggressiveness.[19] Similarly, endometrial carcinomas with mixed histologic features were also classified as serous/serous-like if a serous component was present, because the Cancer Genome Atlas Research Network recently demonstrated that most of these cases cluster in the copy-number high (serous-like) group.[20] Observed cases were categorized in the same way based on pathologic reports, and in cases with available tumor specimens, review of primary tumor by the study pathologist (R.A.S.).

Exact 2-sided *P* values for observed to expected (O:E) ratios for cancers were calculated assuming a Poisson distribution of the observed values using the STATA statistical package (version 13; StataCorp). Confidence intervals were calculated for the lower and upper 2.5% limits compatible with the observed values. The cumulative risk through age 70 years for

developing an incident uterine cancer, assuming the participant underwent RRSO at age 45 years, was estimated by 2 methods, first assuming a constant annual risk and second assuming a constant relative risk compared with SEER rates. In the first approach, annual risk was determined by dividing the number of uterine cancers observed by the number of woman-years of observation. This annual risk was then multiplied by the number of years at risk (ie, 25). In the second approach, age-specific SEER incidence rates were multiplied by the relevant O:E ratio. These absolute risks, starting at age 45 years, were then summed through age 70 years. Analyses stratified by *BRCA1/2* mutation type, breast cancer history, and prior tamoxifen exposure were also performed.

Immunohistochemical Analysis for BRCA1 Protein Expression

For uterine cancer cases from *BRCA1*+ women, available tumor specimens were analyzed for BRCA1 protein expression, as previously described.[21] Briefly, the study pathologist assessed immunohistochemical staining intensity relative to an internal positive control. Loss of BRCA1 protein expression was predefined as less than 5% of cells staining with a positive internal control, whereas staining of greater than 10% was considered retention of BRCA1 protein expression.

Loss of Heterozygosity Analysis

For uterine cancer cases with available tumor, microdissected tumor and normal DNA were extracted from archival material and amplified using mutation-specific primers. Loss of heterozygosity was determined by comparing fragment distributions between normal and tumor amplicons.[22] Loss of heterozygosity was predefined as a reduction of greater than 50% of the wild-type allele at the site of the germline mutation in the tumor sample.

RESULTS

Of 1083 women who met the final eligibility criteria, 627 (57.9%) were *BRCA1*+, 453 (41.8%) were *BRCA2*+, and 3 (0.3%) had mutations in both genes. The median age at RRSO was 45.6 (interquartile range [IQR], 40.9–52.5) years and the median follow-up was 5.1 (IQR, 3.0–8.4) years. Seven hundred twenty-seven study participants (67.1%) had a history of breast cancer, and 273 of the 928 women (29.4%) with data available had used tamoxifen (eTable 2 in the Supplement).

During 6377 woman-years of follow-up, 8 women developed uterine cancer (O:E ratio, 1.9; 95% CI, 0.8–3.7; $P = .09$) (Table 1 and eTable 3 in the Supplement). Two women developed endometrioid carcinoma (1 with International Federation of Gynecology and Obstetrics grade 1 and 1 with grade 2) (O:E ratio, 0.6; 95% CI, 0.1–2.0; $P = .88$), both within 3 years of RRSO. One woman developed leiomyosarcoma (O:E ratio, 7.1; 95% CI, 0.2–39.4; $P = .13$) 1.4 years after RRSO. Five serous/serous-like endometrial carcinomas (1 high-grade carcinoma with serous and undifferentiated components; 1 high-grade carcinoma with serous and endometrioid features; 1 carcinosarcoma with a serous epithelial component; 1 serous carcinoma with an undifferentiated component; and 1 pure serous carcinoma) were observed (O:E ratio, 14.8; 95% CI, 4.8–34.6; $P < .001$), 7.2 to 12.9 years after RRSO.

Five of 627 *BRCA1*+ women developed uterine cancer (2.38 expected; O:E ratio, 2.1; 95% CI, 0.7–4.9; $P = .09$) during 3781 woman-years. Four serous/serous-like carcinomas (0.18 expected; O:E ratio, 22.2; 95% CI, 6.1–56.9; $P < .001$) (Table 2) and 1 sarcoma (0.08 expected; O:E ratio, 12.4; 95% CI, 0.3–69.3; $P = .08$) developed. With use of these data, the estimated risk for developing serous/serous-like carcinoma through age 70 years for a *BRCA1*+ woman undergoing RRSO at age 45 years was 2.6% (95% CI, 0.7%–6.8%), assuming a constant annual risk, and 4.7% (95% CI, 1.3%–12.1%), assuming a constant relative risk compared with SEER rates.

Three of 453 *BRCA2*+ women developed uterine carcinoma (1.91 expected; O:E ratio, 1.6; 95% CI, 0.3–4.6; $P = .30$) during 2580 woman-years. Two endometrioid cases (1.60 expected; O:E ratio, 1.2; 95% CI, 0.2–4.5; $P = .48$) and 1 serous/serous-like case (0.16 expected; O:E ratio, 6.4; 95% CI, 0.2–35.5; $P = .15$) developed.

Four of five serous/serous-like carcinomas occurred in women with prior breast cancer, 3 of whom used tamoxifen (eTable 3 in the Supplement). One woman with a history of breast cancer without tamoxifen use developed leiomyosarcoma. All women with serous/serous-like carcinoma or sarcoma received adjuvant chemotherapy and/or radiotherapy. Two of 5 women with serous/serous-like carcinoma have had disease recurrence, 1.6 and 2.0 years after diagnosis, and one ultimately died of the disease.

Immunohistochemistry Analysis

Tumor tissue from 3 of 5 serous/serous-like carcinomas and the leiomyosarcoma were available. All of these occurred in *BRCA1*+ women. When BRCA1 protein expression was examined, all 3 serous/serous-like carcinomas demonstrated loss of protein expression compared with intact internal control (Figure, A–C). The leiomyosarcoma, however, retained BRCA1 protein expression (Figure, D).

Loss of Heterozygosity Analysis

Two of 3 available serous/serous-like carcinomas demonstrated loss of the wild-type *BRCA1* allele (patients A and B, eFigure in the Supplement). The other available serous/serous-like carcinoma and the leiomyosarcoma retained the wild-type *BRCA1* allele (patients C and D, eFigure in the Supplement).

Analysis Stratified for Personal History of Breast Cancer and Prior Tamoxifen Use

Given that only the serous/serous-like subtype was observed more frequently than expected, we limited the following analyses to the serous/serous-like subtype tumors. We observed 4 serous/serous-like carcinomas in 727 women with prior breast cancer (0.26 expected; O:E ratio, 15.5; 95% CI, 4.2–39.7; $P < .001$). One serous/serous-like carcinoma was seen in 356 women without prior breast cancer (0.08 expected; O:E ratio, 12.6; 95% CI, 0.3–70.3; $P = .08$). Three serous/serous-like carcinomas were seen in 273 tamoxifen-exposed women (0.12 expected; O:E ratio, 24.4; 95% CI, 5.0–71.3; $P < .001$). Two serous/serous-like carcinomas occurred in 655 women without prior tamoxifen use (0.18 expected; O:E ratio, 11.3; 95% CI, 1.4–40.8; $P = .01$) (Table 2).

DISCUSSION

These results suggest that *BRCA1*+ women undergoing RRSO without hysterectomy remain at increased risk for serous/serous-like endometrial carcinoma. The lack of BRCA1 protein expression in all 3 available *BRCA1*-associated serous/serous-like specimens and the loss of the wild-type *BRCA1* allele in 2 of 3 available tumors support the biologic plausibility that the loss of *BRCA1* function was important in the tumorigenesis of the serous/serous-like cancers seen in our cohort.

Whether uterine cancer is a *BRCA*-associated tumor has long been controversial. The Breast Cancer Linkage Consortium showed an increased risk for uterine cancer in *BRCA1*+ women (relative risk, 2.65; 95% CI, 1.69–4.16; $P < .001$), but not in *BRCA2*+ women.[8,9] Similarly, Segev et al[10] found an increased risk for endometrial cancer for *BRCA1*+ women (standardized incidence ratio,1.91; 95% CI, 1.06–3.19; $P = .03$). However, this risk may have been limited to tamoxifen-exposed women. Importantly, neither study commented on the histologic subtypes of these cancers.

Several studies have also evaluated the potential association between serous endometrial carcinoma and *BRCA* mutations. In 2000, Goshen et al[13] examined 56 patients with serous endometrial carcinoma and did not identify any *BRCA* mutations. However, only selective founder and protein-truncating mutations in exon 11 of *BRCA1* and exons 10 and 11 of *BRCA2* were examined. In 2001, Levine et al[14] similarly did not find any founder *BRCA* mutations in 21 serous/serous-like endometrial carcinomas from individuals of Jewish heritage. However, 2 independent Israeli studies[11,12] since reported that 4 of 31 (12.9%) and 7 of 59 (11.9%) consecutive Jewish patients with serous endometrial carcinoma, respectively, carried a *BRCA1* mutation. Also, a recent multi-institutional study identified nonfounder *BRCA1* mutations in 3 of 151 unselected patients (2.0%) with serous endometrial carcinoma.[23] When all 5 studies to date are pooled, 3 of 207 serous/serous-like carcinomas in admixed US and Canadian patients (1.4%) and 11 of 111 serous/serous-like carcinomas in US and Israeli Jews (9.9%) had a detectable *BRCA1* mutation (eTable 4 in the Supplement). This finding is in contrast to the 0.12% to 0.29% and 1.1% to 1.2% expected mutation rates in these respective populations.[24]

In the only other prospective study analyzing the risk for uterine cancer after RRSO in *BRCA* mutation carriers with complete histologic information available, 2 endometrioid carcinomas developed during 6 years of follow-up in 315 *BRCA*+ women. No serous/serous-like carcinomas or sarcomas were seen.[25] However, patients could be ascertained and followed up before genetic testing, which could result in underestimation of risk in aggressive cancers such as serous carcinoma. Furthermore, that study included 70% fewer *BRCA1*+ women, with a median age at RRSO 3 years younger than in our report, which potentially limits the previous study's power to detect an increased incidence of serous/serous-like endometrial carcinoma.

In our study, all 3 *BRCA1*-associated serous/serous-like carcinomas with available tissue showed clear loss of BRCA1 protein expression. In 2 cases, we also demonstrated that loss of the wild-type *BRCA1* allele was the likely cause. In the third case, the mechanism for

protein expression loss was not elucidated. This result may be analogous to the situation in *BRCA*-associated serous ovarian cancer, in which 19% to 28% of *BRCA*-associated ovarian cancers do not demonstrate loss of heterozygosity,[26] suggesting other mechanisms of *BRCA* silencing are important in a significant percentage of *BRCA*-associated disease.

Recent investigations have proposed that most serous ovarian cancers originate from the fallopian tubes.[27,28] Given this hypothesis, there is speculation that some serous endometrial cancers may be metastases from concomitant tubal primary tumors. However, for most cases with coexisting serous cancers in the fallopian tube and endometrium, the endometrial component appears to be superficial or noninvasive.[29] In contrast, all serous/serous-like carcinomas in our series presented with myoinvasive disease no fewer than 7 years after RRSO, arguing against these being tubal metastases. Further, the fallopian tubes and endometrium share an embryological precursor, the paramesonephric (Müllerian) ducts. It is therefore plausible the endometrium may be susceptible to similar *BRCA*-mediated carcinogenesis as the fallopian tube.

Possible confounding by a history of breast cancer and/or tamoxifen exposure remains a consideration. Several studies have suggested that women with serous endometrial carcinoma are more likely to have a personal or a family history of breast cancer than women without cancer[30] or women with endometrioid carcinoma.[31,32] The cause of this association is unclear, but as none of these studies have examined *BRCA* mutation status, the association may be explained in part by *BRCA1* mutations. The relationship between tamoxifen exposure and serous/serous-like endometrial carcinoma is less clear[33]; however, recent reports have suggested an association.[34,35] While tamoxifen exposure cannot explain the loss of the wild-type *BRCA1* allele seen in 2 of the 3 available serous/serous-like tumors in our series, it may act as a risk modifier in the presence of decreased BRCA1 protein expression, as posited by Wen et al.[36] Given this possibility, tamoxifen exposure may account for some of the serous-like carcinoma risk seen in our report.

Although this report is, to our knowledge, the largest prospective study to date, relatively few events were observed. Given this, we have estimated the penetrance of serous/serous-like cancer through age 70 years in women with *BRCA1* mutations using 2 approaches. In the first approach, we assumed a constant relative risk of 22.2 compared with SEER rates from ages 45 through 70 years. We also took a more conservative approach and assumed a constant annual risk for serous/serous-like endometrial cancer of 1.06 per 1000 woman-years (4 cases observed in 3781 woman-years). Although future studies will be required to determine which of these approaches is most appropriate, both approaches estimate a risk for serous/serous-like endometrial cancer through age 70 years of at least 2.6%, which is likely clinically important given the high morbidity and mortality rates for serous/serous-like disease. Misclassification and/or underreporting of rare uterine cancer subtypes in SEER is also possible, which could lead to inflation of our O:E ratios. However, this possibility is unlikely to be a major effect, as 10.3% of uterine cancers reported in SEER are serous/serous-like, consistent with other epidemiologic studies.[37] In addition, bias could have been introduced because we excluded cases from SEER with unknown histologic subtypes from our calculated expected rates. Such cases only accounted for 0.77% of the total corpus cancers in SEER and therefore are unlikely to substantially alter our results. Because we

only had 1 *BRCA2*-related serous event in our study, we cannot conclusively comment on whether *BRCA2*+ women have a significantly increased risk for serous/serous-like endometrial carcinoma, and the answer to this question awaits further studies.

Although abdominal hysterectomy with bilateral salpingo-oophorectomy is clearly associated with increased complications and costs compared with RRSO alone, comparison of complications and costs may be more appropriate when both hysterectomy and RRSO are performed via a minimally invasive (laparoscopic or robotic) approach. In 2 recent analyses of data from the Perspective database (Premier, Inc), 5.3% of 4971 women undergoing laparoscopic hysterectomy had an intraoperative, surgical site, or medical complication.[38] This rate was similar to the 6.0% complication rate of 3632 women undergoing laparoscopic oophorectomy.[39] Laparoscopic hysterectomy was more expensive to perform, with a median total cost of $6679 compared with $4737 for laparscopic oophorectomy.[38,39] Because the number of hysterectomies necessary to prevent 1 serous cancer case during 25 years of follow-up ranges from 21.2 to 37.9, an incremental cost ranging from $41170 to $73601 to prevent 1 serous cancer case would likely be considered reasonable. Other potential long-term complications of hysterectomy include urinary incontinence and pelvic prolapse, although the risk for these seems greatest in women with preexisting pelvic support defects.[40,41] It remains controversial whether hysterectomy has an adverse effect on sexual function.[42] However, for *BRCA1*+ women undergoing premenopausal RRSO, the most important factor affecting sexual function, irrespective of uterine management, is almost certainly the induction of surgical menopause. Last, mortality due to hysterectomy is very rare and much lower than would be expected for serous uterine cancer in this cohort, having been reported as 0.03% to 0.06% in 3 population-based studies from Finland, the United Kingdom, and Australia, which together reported on more than 126000 hysterectomies performed for nonmalignant indications.[43–45]

Given the similar surgical risks, very low mortality, acceptable costs, and potential protection against serous-like endometrial cancer, if the present results are confirmed by future studies, hysterectomy with bilateral salpingo-oophorectomy may become the preferred risk-reducing surgical approach for *BRCA1*+ women. However, even if these results are confirmed, RRSO alone may still have a role for *BRCA1*+ women if strong reasons exist for uterine retention, such as dense pelvic adhesions or desire for future pregnancy using assisted reproductive approaches. For *BRCA1*+ women who have already undergone RRSO, the optimal approach is less clear. Whether a 25-year risk for serous/serous-like uterine cancer of 2.6% to 4.7% justifies the risks and costs of a second surgery will need to be addressed by future prospective studies.

CONCLUSIONS

Our results suggest that *BRCA1*+ women are at increased risk for serous/serous-like endometrial carcinoma. Although instability in the estimated magnitude of this risk remains, we believe that the possibility of this cancer should be considered when discussing the advantages and risks of hysterectomy at the time of RRSO in *BRCA1*+ women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support: This study was supported in part by the Department of Defense Ovarian Cancer Research Program (DAMD17-03-1-0375 to N.D.K.); the National Institute of Health (R01-CA083855 and R01-CA102776 to T.R.R); NIH/NCI Cancer Center Support Grants (P30 CA008748, P30 CA016520, P30 CA51008, P30 CA16042); the Prevention, Control, and Population Research Program of Memorial Sloan Kettering Cancer Center; Project Hope for Ovarian Cancer Research and Education; Eisenberg-Feinstein Fund for Gynecological Cancer Research and Treatment; Chia Family Foundation; Andrew Sabin Family Foundation; Filomena M. D'Agostino Foundation; National Institute for Health Research to the Biomedical Research Centre at the Institute of Cancer Research; Royal Marsden NHS Foundation Trust; Susan G. Komen for the Cure; Basser Center for BRCA; and the Breast Cancer Research Foundation.

Role of the Funders/Sponsors: The funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

References

1. Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a *BRCA1* or *BRCA2* mutation. N Engl J Med. 2002; 346(21):1609–1615. [PubMed: 12023992]
2. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prevention and Observation of Surgical End Points Study Group. Prophylactic oophorectomy in carriers of *BRCA1* or *BRCA2* mutations. N Engl J Med. 2002; 346(21):1616–1622. [PubMed: 12023993]
3. Kauff ND, Domchek SM, Friebel TM, et al. Risk-reducing salpingo-oophorectomy for the prevention of *BRCA1*- and *BRCA2*-associated breast and gynecologic cancer. J Clin Oncol. 2008; 26(8):1331–1337. [PubMed: 18268356]
4. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in *BRCA1* or *BRCA2* mutation carriers with cancer risk and mortality. JAMA. 2010; 304(9):967–975. [PubMed: 20810374]
5. Finch AP, Lubinski J, Møller P, et al. Impact of oophorectomy on cancer incidence and mortality in women with a *BRCA1* or *BRCA2* mutation. J Clin Oncol. 2014; 32(15):1547–1553. [PubMed: 24567435]
6. American College of Obstetricians and Gynecologists; ACOG Committee on Practice Bulletins–Gynecology; ACOG Committee on Genetics; Society of Gynecologic Oncologists. ACOG Practice Bulletin No. 103. Obstet Gynecol. 2009; 113(4):957–966. [PubMed: 19305347]
7. Kauff ND, Barakat RR. Risk-reducing salpingo-oophorectomy in patients with germline mutations in *BRCA1* or *BRCA2*. J Clin Oncol. 2007; 25(20):2921–2927. [PubMed: 17617523]
8. Thompson D, Easton DF, Breast Cancer Linkage Consortium. Cancer incidence in *BRCA1* mutation carriers. J Natl Cancer Inst. 2002; 94(18):1358–1365. [PubMed: 12237281]
9. Breast Cancer Linkage Consortium. Cancer risks in *BRCA2* mutation carriers. J Natl Cancer Inst. 1999; 91(15):1310–1316. [PubMed: 10433620]
10. Segev Y, Iqbal J, Lubinski J, et al. Hereditary Breast Cancer Study Group. The incidence of endometrial cancer in women with *BRCA1* and *BRCA2* mutations. Gynecol Oncol. 2013; 130(1): 127–131. [PubMed: 23562522]
11. Bruchim I, Amichay K, Kidron D, et al. *BRCA1/2* germline mutations in Jewish patients with uterine serous carcinoma. Int J Gynecol Cancer. 2010; 20(7):1148–1153. [PubMed: 21206239]
12. Lavie O, Ben-Arie A, Segev Y, et al. *BRCA* germline mutations in women with uterine serous carcinoma. Int J Gynecol Cancer. 2010; 20(9):1531–1534. [PubMed: 21119368]
13. Goshen R, Chu W, Elit L, et al. Is uterine papillary serous adenocarcinoma a manifestation of the hereditary breast-ovarian cancer syndrome? Gynecol Oncol. 2000; 79(3):477–481. [PubMed: 11104623]

14. Levine DA, Lin O, Barakat RR, et al. Risk of endometrial carcinoma associated with *BRCA* mutation. Gynecol Oncol. 2001; 80(3):395–398. [PubMed: 11263938]
15. Moore KN, Fader AN. Uterine papillary serous carcinoma. Clin Obstet Gynecol. 2011; 54(2):278–291. [PubMed: 21508697]
16. Domchek SM, Friebel TM, Neuhausen SL, et al. Mortality after bilateral salpingo-oophorectomy in *BRCA1* and *BRCA2* mutation carriers. Lancet Oncol. 2006; 7(3):223–229. [PubMed: 16510331]
17. National Cancer Institute Surveillance, Epidemiology, and End Results Program. SEER*Stat Databases: November 2012 Submission. Incidence—SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2012 Sub (2000–2010). <Katrina/Rita Population Adjustment>. http://seer.cancer.gov/data/seerstat/nov2012/. Released April 2013. Accessed August 27, 2015
18. Centers for Disease Control and Prevention (CDC). Behavioral Risk Factor Surveillance System Survey Data. Atlanta, Georgia: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2010.
19. Cantrell LA, Blank SV, Duska LR. Uterine carcinosarcoma. Gynecol Oncol. 2015; 137(3):581–588. [PubMed: 25805398]
20. Kandoth C, Schultz N, Cherniack AD, et al. Cancer Genome Atlas Research Network. Integrated genomic characterization of endometrial carcinoma. Nature. 2013; 497(7447):67–73. #x0005B;published correction in Nature. 2013 Aug 8;500(7461):242]. [PubMed: 23636398]
21. Garg K, Levine DA, Olvera N, et al. *BRCA1* immunohistochemistry in a molecularly characterized cohort of ovarian high-grade serous carcinomas. Am J Surg Pathol. 2013; 37(1):138–146. [PubMed: 23232854]
22. Brozek I, Ochman K, Debniak J, et al. Loss of heterozygosity at *BRCA1/2* loci in hereditary and sporadic ovarian cancers. J Appl Genet. 2009; 50(4):379–384. [PubMed: 19875889]
23. Pennington KP, Walsh T, Lee M, et al. *BRCA1*, *TP53*, and *CHEK2* germline mutations in uterine serous carcinoma. Cancer. 2013; 119(2):332–338. [PubMed: 22811390]
24. Whittemore AS, Gong G, Itnyre J. Prevalence and contribution of *BRCA1* mutations in breast cancer and ovarian cancer. Am J Hum Genet. 1997; 60(3):496–504. [PubMed: 9042908]
25. Reitsma W, Mourits MJ, de Bock GH, Hollema H. Endometrium is not the primary site of origin of pelvic high-grade serous carcinoma in *BRCA1* or *BRCA2* mutation carriers. Mod Pathol. 2013; 26(4):572–578. [PubMed: 23080033]
26. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011; 474(7353):609–615. [PubMed: 21720365]
27. Levanon K, Crum C, Drapkin R. New insights into the pathogenesis of serous ovarian cancer and its clinical impact. J Clin Oncol. 2008; 26(32):5284–5293. [PubMed: 18854563]
28. Kurman RJ, Shih IeM. The origin and pathogenesis of epithelial ovarian cancer. Am J Surg Pathol. 2010; 34(3):433–443. [PubMed: 20154587]
29. Jarboe EA, Miron A, Carlson JW, et al. Coexisting intraepithelial serous carcinomas of the endometrium and fallopian tube. Int J Gynecol Pathol. 2009; 28(4):308–315. [PubMed: 19483636]
30. Slomovitz BM, Burke TW, Eifel PJ, et al. Uterine papillary serous carcinoma (UPSC). Gynecol Oncol. 2003; 91(3):463–469. [PubMed: 14675663]
31. Chan JK, Manuel MR, Cheung MK, et al. Breast cancer followed by corpus cancer. Gynecol Oncol. 2006; 102(3):508–512. [PubMed: 16483640]
32. Liang SX, Pearl M, Liang S, et al. Personal history of breast cancer as a significant risk factor for endometrial serous carcinoma in women aged 55 years old or younger. Int J Cancer. 2011; 128(4): 763–770. [PubMed: 20473885]
33. Barakat RR, Wong G, Curtin JP, Vlamis V, Hoskins WJ. Tamoxifen use in breast cancer patients who subsequently develop corpus cancer is not associated with a higher incidence of adverse histologic features. Gynecol Oncol. 1994; 55(2):164–168. [PubMed: 7959278]
34. Bland AE, Calingaert B, Secord AA, et al. Relationship between tamoxifen use and high risk endometrial cancer histologic types. Gynecol Oncol. 2009; 112(1):150–154. [PubMed: 18937966]
35. Brinton LA, Felix AS, McMeekin DS, et al. Etiologic heterogeneity in endometrial cancerl. Gynecol Oncol. 2013; 129(2):277–284. [PubMed: 23485770]

36. Wen J, Li R, Lu Y, Shupnik MA. Decreased *BRCA1* confers tamoxifen resistance in breast cancer cells by altering estrogen receptor-coregulator interactions. Oncogene. 2009; 28(4):575–586. [PubMed: 18997820]
37. Fader AN, Boruta D, Olawaiye AB, Gehrig PA. Uterine papillary serous carcinoma. Curr Opin Obstet Gynecol. 2010; 22(1):21–29. [PubMed: 19952744]
38. Wright JD, Ananth CV, Lewin SN, et al. Robotically assisted vs laparoscopic hysterectomy among women with benign gynecologic disease. JAMA. 2013; 309(7):689–698. [PubMed: 23423414]
39. Wright JD, Kostolias A, Ananth CV, et al. Comparative effectiveness of robotically assisted compared with laparoscopic adnexal surgery for benign gynecologic disease. Obstet Gynecol. 2014; 124(5):886–896. [PubMed: 25437715]
40. Altman D, Granath F, Cnattingius S, Falconer C. Hysterectomy and risk of stress-urinary-incontinence surgery. Lancet. 2007; 370(9597):1494–1499. [PubMed: 17964350]
41. Dällenbach P, Kaelin-Gambirasio I, Dubuisson JB, Boulvain M. Risk factors for pelvic organ prolapse repair after hysterectomy. Obstet Gynecol. 2007; 110(3):625–632. [PubMed: 17766610]
42. Lonnée-Hoffmann R, Pinas I. Effects of hysterectomy on sexual function. Curr Sex Health Rep. 2014; 6(4):244–251. [PubMed: 25999801]
43. Mäkinen J, Johansson J, Tomás C, et al. Morbidity of 10 110 hysterectomies by type of approach. Hum Reprod. 2001; 16(7):1473–1478. [PubMed: 11425832]
44. McPherson K, Metcalfe MA, Herbert A, et al. Severe complications of hysterectomy. BJOG. 2004; 111(7):688–694. [PubMed: 15198759]
45. Spilsbury K, Hammond I, Bulsara M, Semmens JB. Morbidity outcomes of 78577 hysterectomies for benign reasons over 23 years. BJOG. 2008; 115(12):1473–1483. [PubMed: 19035986]

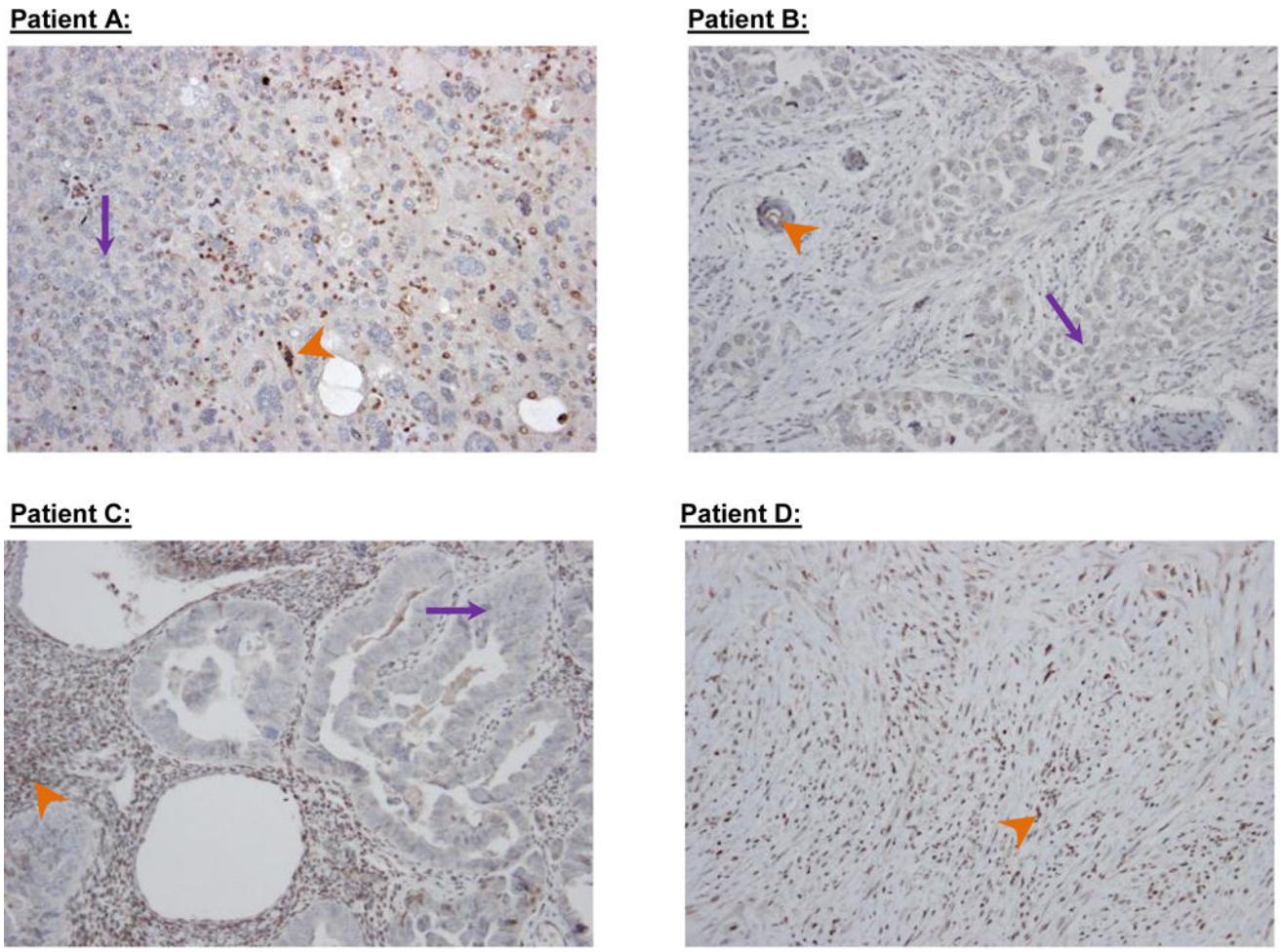

Figure 1. Immunohistochemical (IHC) evaluation of BRCA1 protein expression for uterine corpus cancers that developed during follow-up

Patient A – Serous-like Carcinoma: IHC evaluation shows loss of BRCA1 protein expression in tumor cell nuclei compared to an intact internal control (tumor infiltrating lymphocytes). **Patient B – Serous-like Carcinoma:** IHC again demonstrates **l**oss of BRCA1 protein expression in tumor cell nuclei compared to an intact internal control (perivascular smooth muscle). **Patient C – Serous-like Carcinoma:** IHC demonstrates lack of staining in tumor cell nuclei compared to an intact internal control (endometrial stroma). **Patient D - Leiomyosarcoma:** IHC shows retention of BRCA1 protein expression.

Table 1

Observed and expected rates for uterine corpus cancer in *BRCA* mutation carriers

	Expected	Observed	O/E	95% Confidence Interval of the O/E	p
All Corpus Cancers	4.30	8	1.86	0.80 – 3.67	0.09
Endometrioid carcinoma	3.62	2	0.55	0.07 – 1.99	0.88
Serous/serous-like carcinoma	0.34	5	14.8	4.81 – 34.6	<0.001
Sarcoma	0.14	1	7.07	0.18 – 39.4	0.13

Table 2

Observed and expected rates for serous/serous-like endometrial cancer in *BRCA* mutation carriers

	Expected	Observed	O/E	95% Confidence Interval of the O/E	p	Follow Up (Woman-Years)
All Participants (N=1083)	0.34	5	14.8	4.81 – 34.6	<0.001	6376.5
BRCA1 (N=627)	0.18	4	22.2	6.05 – 56.9	<0.001	3781.0
BRCA2 (N=453)	0.16	1	6.37	0.16 – 35.5	0.15	2579.7
Prior Breast Cancer						
Yes (N=727)	0.26	4	15.5	4.22 – 39.7	<0.001	4434.7
No (N=356)	0.08	1	12.6	0.32 – 70.3	0.08	1941.8
Tamoxifen Exposure						
Yes (N=273)	0.12	3	24.4	5.03 – 71.3	<0.001	1878.8
No (N=655)	0.18	2	11.3	1.37 – 40.8	0.01	3738.8