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Role of prophylactic hysterectomy in patients at high risk for hereditary cancers

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Abstract

Background. Current surgical recommendations for ovarian cancer prophylaxis in women at high risk of developing ovarian cancer include bilateral salpingo-oophorectomy (risk-reducing salpingo-oophorectomy (RRSO)). The role of hysterectomy is unclear. We sought to determine outcomes following prophylactic surgery in high-risk women.

Methods. We surveyed unaffected members of the Gilda Radner Familial Ovarian Cancer Registry who had undergone oophorectomy from 1981 to 2002. Data were collected and analyzed for statistical significance by the Fisher's Exact Test.

Results. Two hundred eighty women were surveyed, and 154 (55%) responded; 97% were Caucasian and 14% reported being Jewish. The median age of the respondents was 51 years (range 29–79); median age at oophorectomy was 41 years (range 15–68). Fifty-eight patients (38%) reported a laparoscopic procedure. One hundred five patients (68%) had a simultaneous hysterectomy, and 4 (3%) had a prior hysterectomy. Forty-four patients (29%) underwent BSO only. Of these 44 patients, 40 (91%) did not require a subsequent hysterectomy. Of the 4 who did, 2 were for leiomyomas, one for menorrhagia and the other was unknown. While not statistically significant, of the 3 patients who developed a subsequent gynecologic malignancy, all had undergone a hysterectomy. There was a statistically significant difference in whether or not the uterus was removed as part of the procedure by time period, whereby women treated prior to 1990 had a higher likelihood of having a hysterectomy ($P = 0.03$).

Conclusion. The women in our study did not require hysterectomy for prevention of malignancy. We conclude that one should screen for benign gynecological indications for hysterectomy when planning a prophylactic BSO for prevention of ovarian cancer. Other potential risk factors for endometrial cancer, including the role of UPSC in HBOC, remain to be elucidated.

Keywords: Familial ovarian cancer; Prophylactic oophorectomy; Hysterectomy

Introduction

The lifetime risk of developing ovarian cancer in the general population is 1–2%. For women with a family history of ovarian cancer, their lifetime risk of developing this disease increases to 4 to 5% with one first degree relative and to 7% when 2 first-degree relatives are affected [1,2]. The lifetime risk of ovarian cancer in women belonging to HBOC (Hereditary Breast and Ovarian Cancer Syndrome) families is 40–60% [3]. Increased awareness of a genetic component to this disease has led to formation of ovarian cancer registries [4]. Registries and clinics specific to hereditary ovarian cancer syndromes have been the source of high-risk patient cohorts used to test risk-reducing strategies. These strategies include increased surveillance (bimanual pelvic exams, pelvic ultrasound with color flow Doppler and serial serum CA-125 levels), oral contraceptive pills and risk-reducing salpingo-oophorectomy (RRSO). The National Institute of Health consensus statement states that the risk of ovarian cancer in women from families with HBOC

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syndromes is sufficiently high to recommend RRSO in women at age 35 or after childbearing is completed [5,6]. These recommendations additionally advise that women undergoing RRSO should be informed that removal of the tubes and ovaries does not provide 100% protection and that they remain at risk of primary peritoneal carcinoma [7].

Current recommendations for risk reduction include prophylactic bilateral salpingo-oophorectomy in women at high risk for developing ovarian cancer [8]. Controversy regarding the recommendations for the type of prophylactic surgery offered women arises with the question "is hysterectomy a necessary component of the prophylactic surgery?" Proponents argue that it reduces incidence of future gynecologic surgery, risk of fallopian tube cancer and risk of papillary serous carcinoma of the uterus and simplifies hormone replacement therapy. Those in opposition counter that it increases morbidity, operative time, hospital stay, recovery time and overall costs. Our objective in this study was to evaluate actual practice patterns in women at risk who had undergone RRSO. We also sought to determine the outcome of those women who did not have hysterectomy as part of their initial procedure.

Materials and methods

This study invited participation, via questionnaire, of 280 women in the Gilda Radner Familial Ovarian Cancer Registry (GRFOCR) who had undergone previous oophorectomy from 1981 to 2002. Inclusion in the Registry requires a family history of ovarian cancer and the majority of women had at least 2 close (1st or 2nd degree) relatives with ovarian cancer. In addition to demographic information, indications for hysterectomy, incidence of hysterectomy and the incidence of subsequent gynecological cancers following prophylactic surgery were collected. The Registry routinely pursues the pathology report and medical records of all reported malignancies to confirm diagnoses. If there was no cancer history, this was not performed.

Categorical data were analyzed using Fisher's Exact Test. Patients were stratified based on whether or not a hysterectomy was performed coincident with the oophorectomy. Comparisons were made between these two patient subsets for proportions of subsequent gynecologic malignancy (yes or no), surgery type for complications (bowel obstruction, bowel resection, colon resection or exploratory) and era of diagnosis (in 5-year intervals). The null hypothesis in each of these comparisons was that there were equal proportions between the two patient subsets for each level of the variable of interest. The two-sided alternative hypothesis was that the proportion in one patient subset was much larger or smaller than in the other subset. Statistical significance was defined to be a P value <0.05. Data analysis was performed using the StatXact5 software package. Ninety-five percent confidence intervals are stated where appropriate.

Results

A total of 154 (55%) women responded to the one time mailing of the survey. The median age of the women completing the survey was 51 years (range: 29–79 years). The majority of the women were white (97%), three were Hispanic (2%) and one Native American (1%). Christianity was the most common religion as self reported by 127 women (82%) followed by 21 (14%) who were Jewish and 6 (4%) who were either other religions or unreported religion. Patients were examined by a gynecologist frequently, with 123 (80%) having at least annual pelvic examinations. One hundred and six (69%) patients had a history of oral contraceptive use, and 141 (92%) had a history of a full term pregnancy.

Table 1
Mutation likelihood risk assessment

	Average	Low	High
Shattuck-Eidens (*BRCA1* only)	22%	0.4%	99%
Couch (*BRCA1* only)	25%	0.3%	96%
BRCAPRO	21%	0.1%	100%
Myriad	16%	3%	90%

Table 2
Characteristics of oophorectomy procedure (n = 154)

Characteristic	No. (%)
Ovaries removed	
One	10 (6%)
Both	143 (93%)
Unknown	1 (1%)
Uterus removed	
Yes	105 (68%)
Yes (prior)	4 (3%)
No	44 (29%)
Unknown	1 (1%)
Type of surgery	
Laparotomy	88 (57%)
Laparoscopy	58 (38%)
Vaginal	2 (1%)
Unknown	6 (4%)
Age at oophorectomy (years)	
Median	41
Range	(15, 68)

Because *BRCA* mutation status was unavailable for these patients, four risk models or databases (BRCAPRO, Shattuck-Eidens, Couch and Myriad laboratory data tables) were used for calculating *BRCA1* and *BRCA2* mutation likelihood to help assess the patients' risk for developing ovarian cancer. Eighty-six percent had a *BRCA1* or *BRCA2* mutation likelihood of 7.8% or greater as calculated by at least one of these models (compared to a general population risk of <1%). Using the BRCAPRO model, the average patient in this study had a 21% risk of harboring a mutation in the *BRCA1* or *2* genes. This highlights the high risk status of patients enrolled in this study. Table 1 compares the four models.

The characteristics of the oophorectomy procedure are summarized in Table 2. The median patient age at the time of oophorectomy was 41 years (range: 15–68 years). There were a total of 109 women (71%) who had their uterus removed, including four women whose uterus had been removed previously. Forty-four women (29%) did not have their uterus removed at the time of oophorectomy. Types of surgical procedures included laparotomy (57%), laparoscopy (38%), vaginal (1%) and unknown (4%).

Table 3 documents the incidence of hysterectomy following RRSO. Among the 47 women who did not report prior hysterectomy, 40 (91%, CI: 78%, 97%) had not undergone subsequent hysterectomy at the time of the survey. Four women (9%, CI: 2%, 22%) did have a subsequent hysterectomy, two secondary to uterine myomas, one due to menorraghia and one woman whose reason was unreported. There were 3 women (6%) whose hysterectomy status was unknown.

Table 3
Incidence of hysterectomy following risk-reducing salpingo-oophorectomy (n = 44)

Incidence	No. (%)
No	40 (91%)
Yes	4 (9%)
Reason	
Uterine myomas	2
Menorraghia	1
Unknown	1

Table 4 details the incidence of subsequent gynecologic malignancy, stratified by whether or not the patients received a hysterectomy at the time of oophorectomy. There were no subsequent malignancies identified among those who did not have their uterus removed. In the group of women who had a hysterectomy as part of their prophylactic procedure, 3 (3%) had a subsequent gynecologic malignancy: two peritoneal cancers and one recurrent ovarian carcinoma in a woman who was diagnosed with ovarian cancer at her original surgery. These differences were not statistically significant (two-sided P value = 0.56, Fisher's Exact Test).

Forty-eight women underwent some type of subsequent surgery, mostly for procedures unrelated to the oophorectomy. A total of five women had surgery for bowel obstruction or bowel resection, and four women reported undergoing subsequent exploratory surgery. These data were stratified by whether or not the women had a hysterectomy at the time of the oophorectomy procedure, and there were no statistically significant differences between the two subsets of patients (P value = 0.72, two-sided Fisher's Exact Test).

In stratifying, by 5-year intervals of when the patients received their RRSO, whether or not the women received a hysterectomy at the time of the procedure, we found the following: among the women who retained their uterus, the vast majority (91%) had been treated in 1990 or later: 9 (20%) 1990–1994, 17 (39%) 1995–1999, 14 (32%) 2000–2003. Among those who underwent a hysterectomy, 72% were treated during the same time period: 34 (32%) 1990–1994, 21 (20%) 1995–1999, 21 (20%) 2000–2003. Twenty-five percent of the women who had a hysterectomy at the time of oophorectomy were treated prior to 1990, while among the women who did not undergo a hysterectomy; only 9% were treated prior to 1990. Comparing the women for whom the time period of the oophorectomy procedure was known (n = 146), there was a statistically significant difference in whether or not the uterus was removed as part of the procedure, comparing prior to 1990 versus 1990 or later. A significantly greater percentage of women had their uterus removed prior to 1990 (P value = 0.03, two-sided Fisher's Exact Test).

Discussion

One of the challenges facing those who care for women at increased risk for breast or ovarian cancer is the identification of strategies that may be used to reduce cancer risks or mortality. Health care providers are faced with multiple options, including increased surveillance, chemoprevention and risk-reducing surgery. Much of the evidenced-based medicine regarding these options is retrospective. Given the lack of prospective standardized studies, clinicians search for the most effective strategies to care for these at-risk patients. Carriers of inherited mutations in the *BRCA* genes are thought to have a lifetime risk of developing breast and ovarian cancer of 50–85% and 20–40% respectively [9,10]. Women who carry germ line mutations in the *BRCA1* or *BRCA2* genes may choose to undergo prophylactic oophorectomy to decrease their risk of developing ovarian and breast carcinomas [11,12].

The extent of surgery remains subject to debate. Some authors believe that adding hysterectomy at the time of BSO will prevent the need for future gynecologic surgery, either for benign or malignant reasons. Hysterectomy at the time of RRSO has been recommended by some investigators because it decreases the risk of endometrial cancer in patients using Tamoxifen for breast cancer [13]. Patients suffering from menopausal symptoms following RRSO are also at risk for osteoporosis and may choose to take estrogens. If the uterus is present, combination hormone replacement therapy is warranted for the prevention of endometrial cancer. Recently, it has been shown that this combination therapy may increase breast cancer, pulmonary embolism and stroke incidence [14]. Hysterectomy at the time of RRSO can simplify hormone replacement and may decrease these risks.

An additional argument in favor of hysterectomy at the time of RRSO is the potential prevention of fallopian tube carcinoma. Although the surface area of the fallopian tube is much greater than that of the ovary, the ovary gives rise to malignancy more than 20 times as frequently [15], and primary fallopian tube carcinoma is a rare entity. While about 11% of fallopian tube cancers present with the symptom triad of leukorrhea, pelvic mass and pain [16], the majority are asymptomatic. During the last several years, evidence of a relationship between carcinoma of the fallopian tube and mutations in *BRCA1* or *2* genes has emerged. Initial reports were from case studies, and now newer epidemiologic evidence has focused on retrospective *BRCA* testing on fallopian tube cancers [17]. The Ontario Cancer Registry had 44 patients diagnosed with fallopian tube carcinoma from 1990 to 1998. Five of the 44 cases were positive for a *BRCA1* mutation (11%) and two for a *BRCA2* mutation (5%) [18]. Three of these patients were of Ashkenazi Jewish descent, and only 2 carried a founder mutation. Lu et al. reviewed 50 women at high risk for ovarian cancer who underwent RRSO. Out of 33 whom had a greater than 25% calculated risk of carrying a germ line

Table 4
Incidence of subsequent gynecologic malignancy by initial hysterectomy status

Initial hysterectomy	Subsequent gynecologic malignancy (P = 0.56)		
	Yes	No	Total
Yes	3	103	106
No	0	43	43
Unknown	–	–	5
Total	3	146	154

mutation in either the *BRCA1* or *BRCA2* gene, serial sections of the ovaries and fallopian tubes revealed 3 occult carcinomas, one of which was of the fallopian tube [11]. Another histological review of 30 women who were *BRCA* mutation carriers and underwent an RRSO found 4 occult fallopian tube carcinomas [19].

Carcinoma of the fallopian tube is believed to be part of the clinical spectrum of *BRCA*-associated gynecologic malignancies. While the additional morbidity of adding a hysterectomy to the RRSO is minimal [18,20], we do not believe it is necessary to prevent future malignancies of the fallopian tube. There have been no documented cases of fallopian tube cancer arising in the cornua of a patient who had a prophylactic oophorectomy without hysterectomy. The most common sites of fallopian tube carcinomas are in the ampulla followed by the infundibulum [21–23]. The need for hysterectomy to prevent fallopian tube carcinoma, therefore, remains debatable.

In considering the risks of uterine pathology in patients harboring a *BRCA* mutation, a retrospective cohort of 199 Ashkenazi Jewish women with endometrial cancer revealed only 3 (1.5%) tumors associated with *BRCA1* mutation, an odds ratio of 0.75 (CI 0.24, 2.34; $P = 0.6$). Thus, a mutation in *BRCA* may not confer an increased lifetime risk of endometrial cancer [24]. The biologic mechanisms of uterine papillary serous carcinoma (UPSC) are largely unknown. Case reports have lead to further investigations as to the role of *BRCA* mutations in UPSC. One report documented an Ashkenazi Jewish woman with UPSC and her sister with papillary serous carcinoma of the ovary. Both had a germ line *BRCA1* mutation (5382insC), suggesting a possible genetic link between *BRCA1* mutations and UPSC [25]. An investigation of an Ashkenazi Jewish family with UPSC reported no identified *BRCA1* or *BRCA2* mutations [26]. Another study retrospectively screened 56 women with UPSC, none of whom was Ashkenazi Jewish, using a protein truncation assay believed to identify 70% of mutations occurring in the coding region of the *BRCA* genes. These samples were also tested for the three most common Ashkenazi Jewish founder mutations known to occur in the *BRCA* genes. No mutations were discovered, and the authors concluded that UPSC was not a likely manifestation of the HBOC syndrome [27]. Other groups studying UPSC patients found that 4 out of 20 Ashkenazi Jewish women had *BRCA1* mutations [28] and 3 out of 9 Ashkenazi Jewish women had *BRCA2* mutations. The current data suggest that Ashkenazi Jewish women with *BRCA* mutations may be at risk for UPSC, and therefore this subgroup of patients might benefit from prophylactic hysterectomy [27,28].

Conclusions

Our study found that 9% of the women surveyed required subsequent hysterectomy following their RRSO procedure. Interestingly, among the women known to have a uterus at the time of surgery ($n = 149$), 70% had their uterus removed at the time of oophorectomy, and only 30% did not. Moreover, among the women whose uterus was not removed, there were no subsequent gynecologic malignancies identified, although not statistically significant. Because only a small number of patients developed a subsequent gynecologic malignancy ($n = 3$), these results must be considered anecdotal. There was not a difference in incidence of subsequent bowel, colon or exploratory surgery between these two groups of women. There was, however, a significant difference in hysterectomy being part of the oophorectomy procedure based on the time period when the surgery was performed, whereby women treated prior to 1990 were much more likely to have received a hysterectomy. This may be related to the fact that the American College of Obstetricians and Gynecologists issued guidelines on RRSO in 1994.

While our study is limited by size and the retrospective nature of the survey, we are able to conclude that, while women do not require hysterectomy for prophylaxis of ovarian or fallopian tube cancer, they should be screened for benign gynecological indications for hysterectomy. Furthermore, serial sectioning of these specimens is imperative for complete evaluation and identification of those patients who may harbor occult malignancies and thus will need a full staging procedure and possibly adjuvant treatment [29–32]. Another possible limitation to our study may be that, although all of the patients in the study had extensive pedigree analysis, allowing us to calculate the likelihood of harboring a *BRCA* mutation and therefore confirm their presumed high risk status, we do not have actual *BRCA1* and *2* mutation status knowledge for these patients.

In consideration of hysterectomy as part of a prophylactic procedure, careful distinction should be made for family histories consistent with HNPCC since 5% of endometrial cancers develop in women with a strong hereditary predisposition due to germ line mutations in DNA mismatch repair genes. Perhaps the most provocative question is the role UPSC plays in the Ashkenazi Jewish population, and whether or not these patients might benefit from a prophylactic hysterectomy remains inconclusive.

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