

## Survey article

Hysterectomy at the time of risk-reducing surgery in *BRCA* carriers

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## A B S T R A C T

In this study, women at risk for *BRCA* were surveyed to understand their choice of prophylactic surgery and associated risk of uterine cancers. The study was conducted as an anonymous online web-based survey that assessed personal and family histories and choice of prophylactic surgery. Respondents were targeted through social media groups that bring awareness to hereditary breast and ovarian cancer.

The study cohort included an international group of 601 respondents. The majority were female (99.3%), in their 40s (34.2%), and had completed college or graduate school (68.8%). 87% of respondents carry *BRCA* gene mutation. Of 339 respondents who underwent risk-reducing salpingo-oophorectomy (RRSO), 55.8% had a hysterectomy at time of RRSO. Most common reasons for hysterectomy at time of RRSO included: 39% provider recommendation, 27.6% personal desire, 9.7% benign indications, 1.6% cancer in uterus, 1.1% precancerous uterine lesion, and 21.1% other ( $N = 185$ ). In this cohort, nine were diagnosed with uterine cancer. Three were diagnosed after risk-reducing surgery. Both patients with uterine serous carcinoma were *BRCA1* carriers.

Two thirds of *BRCA* carriers surveyed had undergone RRSO. Of these, more than half had hysterectomy at time of RRSO. One third chose to have hysterectomy based on surgeon recommendation. < 1% (2 out of 258) of *BRCA1* gene mutation carriers reported being diagnosed with uterine serous carcinomas. While this incidence is low, it may be an underestimate based on the limitations of this study. Additional studies are needed to select which patients will benefit from concurrent hysterectomy and RRSO.

## 1. Introduction

Germline mutations in the *BRCA* gene are associated with an increased risk of breast, ovarian, fallopian tube, primary peritoneal, pancreatic, prostate cancer, and melanoma. Risks of breast and ovarian cancer have been well studied in *BRCA* carriers. Between 1 in 300 and 1 in 800 individuals in the general population carry a *BRCA1* or *BRCA2* gene mutation, with certain populations having higher prevalence including Ashkenazi Jews, French Canadians, and Icelanders (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, 2009). Germline mutations in *BRCA1* and *BRCA2* confer a 39–46% and 12–20% respective lifetime risk of ovarian cancer (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, 2009). Risk reducing interventions in this patient population have been shown to be efficacious and are now recommended by multiple clinical guideline groups including the American College of Obstetricians and

Gynecologists (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, 2009), American Society for Clinical Oncology (Robson et al., 2010), Society of Gynecologic Oncology (Lancaster et al., 2007), National Society of Genetic Counselors (Berliner et al., 2013), and European Society for Medical Oncology (Balmaña et al., 2011). For ovarian and fallopian tube cancer risk reduction, prophylactic bilateral salpingo-oophorectomy (RRSO) is recommended between the ages of 35 and 40 and once child-bearing is complete. RRSO is associated with an approximate 80 to 95% risk reduction (Finch et al., 2014).

Recent literature has suggested that there may be an increased risk of uterine serous carcinomas in women with *BRCA* gene mutations, specifically those women with *BRCA1* mutations (Shu et al., 2016). This potential increased risk caused extensive discussion in the field of gynecologic oncology as to whether surgeons should be recommending hysterectomy at the time of prophylactic bilateral salpingo-oophorectomy. There is some evidence that performing a hysterectomy at the time of prophylactic surgery is cost-effective and could lead to

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decreased mortality (Havrilesky et al., 2017). However, at this time, the clinical guidelines endorsed by leading groups in caring for women with BRCA do not include hysterectomy as part of the risk-reducing surgery (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, 2009; Robson et al., 2010; Lancaster et al., 2007; Berliner et al., 2013; Balmaña et al., 2011).

We investigated how patients with BRCA are choosing their risk-reducing surgery and what information they are using to decide in order to provide insight into what factors are considered to be important in this complex decision making process. A second goal was to estimate the incidence of uterine cancer in BRCA carriers.

## 2. Materials and methods

### 2.1. Survey design

We conducted this investigation using a web-based survey through social media to target an international cohort of BRCA positive and BRCA interested individuals (those who have shown interest in the topic and self selected to participate in an online BRCA social media group). The survey included questions to assess respondent demographics, personal and family histories, decision for type of risk-reducing surgery, and counseling received by healthcare providers. All data was self-reported by survey respondents. This survey was submitted to the Institutional Review Board at the Mount Sinai Health system and was deemed to be exempt from review (GCO#1: 16–1960) as no protected health information was collected from the respondents.

### 2.2. Data collection

Two online social media groups were used to target BRCA interested individuals: “BRCA Advanced 101 & 102 Journal Club” and “Beyond the Pink Moon.” In each social media group, group mediators posted the survey and encouraged participation of all group members. Data was collected from July to August 2016 for this cross-sectional analysis. Six hundred and one respondents completed the survey and were included in the statistical analysis.

### 2.3. Statistical analysis

Demographic, clinical and mutation characteristics are reported descriptively using number and percent for categorical measures and mean and standard deviation for continuous measures. Clinical characteristics were compared between those who chose to have a hysterectomy at the time of their salpingo-oophorectomy and those who did not using Chi-Square or Fisher's Exact test as appropriate for categorical measures and *t*-tests for continuous measures. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

## 3. Results

### 3.1. Demographic characteristics

Six hundred and one respondents completed the survey. The mean age of respondents was 45.7 years, with a range of 20 to 74 years. Almost all respondents were female; the remaining respondents included two males and one female to male transgender person. The respondents consisted of an international cohort with the respondents from Europe, Australia, Asia, and Africa (Iceland, France, Germany, the Netherlands, Romania, Poland, Denmark, Bulgaria, Switzerland, Norway, Australia, New Zealand, Singapore, Israel, Taiwan, South Africa.). Additional demographic characteristics are reported in Table 1.

**Table 1**  
Demographic and clinical characteristics of survey respondents.

Demographic variables (sample size)	Percentage
Age (N = 601)	
< 40 years	30.5%
40–49 years	34.2%
50–59 years	26.0%
60–69 years	8.0%
> 70 years	1.3%
Gender (N = 601)	
Female	99.3%
Male	0.5%
Other	0.2%
Race/ethnicity (N = 600)	
White/Caucasian	91.7%
Multiple ethnicity/other	4.0%
Hispanic	2.2%
Black/African-American	0.8%
American Indian or Alaskan Native	0.8%
Asian/Pacific Islander	0.5%
Nation of residence (N = 601)	
United States	66.4%
Canada	9.8%
United Kingdom	13.0%
Ireland	0.3%
France	0.5%
Germany	0.2%
Other	9.8%

### 3.2. Personal and family histories

Eighty-seven percent (n = 487/561) of respondents reported carrying a BRCA gene mutation (40 respondents did not answer this question). Of these, 53% (n = 258) carried BRCA1 mutation, 46% (n = 223) carried BRCA2 mutation, 1% (n = 5) carried a variant of unknown significance, and 0.2% (n = 1) carried both BRCA1 and BRCA2 mutations. Of the remaining respondents 5.7% (n = 32/561) reported being BRCA negative, 4.3% (n = 24/561) not tested, and 3.2% (n = 18/561) “other.” Of those who reported carrying BRCA gene mutations, the average age of BRCA diagnosis was 40.5 years ± 9.9 (39.1 years BRCA1, 42 years BRCA2).

Seventy-three percent were tested for BRCA due to family history, 20% personal history, 2.8% both personal and family histories, and 4.4% other. The majority (58.8%) of respondents were tested because of physician recommendation. Among respondents, 31.5% were diagnosed with breast cancer, 8.5% with ovarian cancer, and 1.3% with fallopian tube cancer.

### 3.3. Hysterectomy at the time of risk-reducing surgery

Of 339 respondents who reported undergoing risk-reducing salpingo-oophorectomy (RRSO), 55.8% had a hysterectomy at time of RRSO. The most common reasons for patients opting to have hysterectomy at time of RRSO included provider recommendation (38.9%) and personal desire to remove uterus to prevent uterine cancer (27.6%) (Fig. 1). Those who chose to have hysterectomy at time of RRSO were compared against those respondents who did not have hysterectomy. This was done by multiple factors including: current age, age at BRCA diagnosis, race, and BRCA status. The only significant difference found was that respondents who endorsed having hysterectomy at time of RRSO were older (at the time of the survey) relative to those who did not (Table 2).

### 3.4. Uterine cancer development

Nine respondents who underwent RRSO reported being diagnosed with uterine cancer (2 serous, 6 endometrioid, 1 placental site trophoblastic tumor). Of these nine, three reported being diagnosed

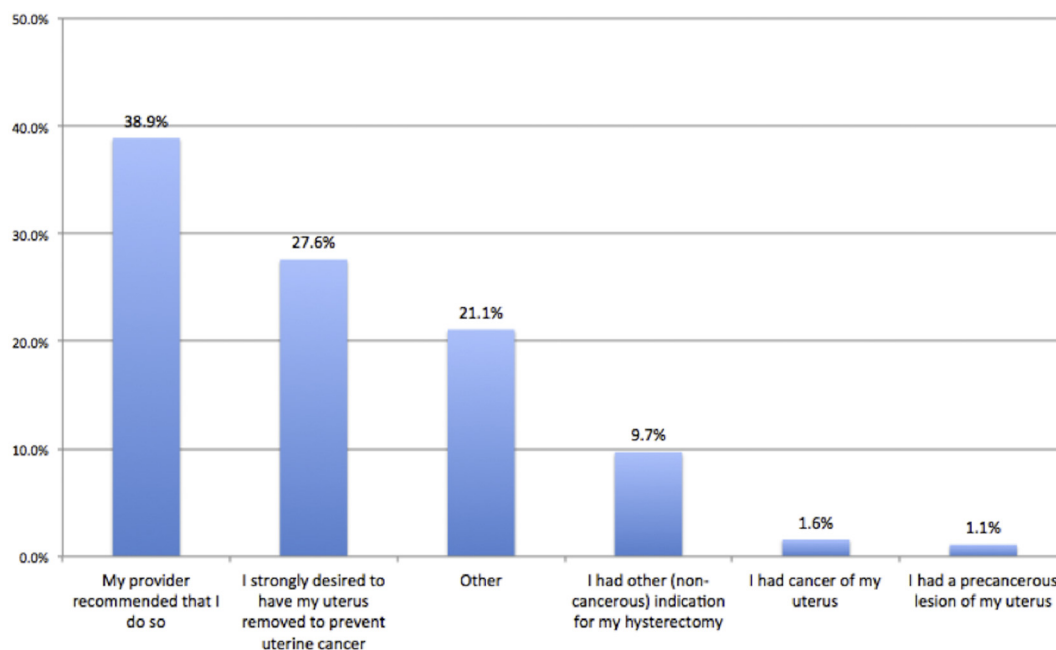


Fig. 1. Reasons for hysterectomy (N = 185 patients) at time of risk-reducing bilateral salpingo-oophorectomy.

subsequent to their prophylactic surgery.

Of note, both patients diagnosed with uterine serous carcinoma were *BRCA 1* carriers. One of the patients with uterine serous carcinoma was diagnosed at time of prophylactic RRSO with hysterectomy and the other was diagnosed many years after RRSO. Survival data was not collected as part of this survey.

#### 4. Discussion

Prophylactic bilateral salpingo-oophorectomy reduces lifetime ovarian cancer risk and maximizes survival in *BRCA* positive women (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, 2009; Kurian et al., 2010). Of the 487 women in our study with a *BRCA* mutation, 63.7% (n = 339) reported having RRSO, consistent with the recommendation for RRSO in *BRCA* positive patients (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, 2009; Robson et al., 2010; Lancaster et al., 2007; Berliner et al., 2013). The question remains unanswered as to whether hysterectomy should be performed as a part of the risk-reducing surgery to prevent uterine cancer. In this study, over half (55.8%) of women reported opting to undergo hysterectomy at the time of RRSO. Most did so because of counseling by their provider (38.9%). Providers are making this recommendation despite it not being part of the clinical guidelines (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, 2009; Robson et al., 2010; Lancaster et al., 2007; Berliner et al., 2013; Balmaña et al., 2011). Providers may be doing so because of the literature supporting the association between uterine serous carcinomas in a subset of *BRCA* patients. A substantial proportion of *BRCA* patients (27.6%) expressed a strong concern for their personal risk of uterine cancer, which led them to having hysterectomy at time of RRSO. Multiple studies have found association between uterine serous carcinoma and *BRCA* mutations (Shu et al., 2016; Lavie et al., 2010; Bruchim et al., 2010; De Jonge et al., 2017); however, other studies have not supported this association (Beiner et al., 2007; Goshen et al.,

2000; Levine et al., 2001). The lifetime risk of an individual with *BRCA1* or *BRCA2* mutation has yet to be well understood.

The incidence of uterine carcinoma is 25.6 cases per 100,000 persons in the United States (American Cancer Society, 2018). In this study, we found 8 cases of uterine cancer and 1 case of placental site trophoblastic tumor in a population of 601 study respondents. Our rate of cancer is higher than that in the general population. This is likely due to the fact that this is a highly specialized population and includes a higher proportion of older women than the general United States population.

Shu et al. found that *BRCA1* patients are at highest risk for development of uterine serous carcinoma; 4 out of 627 developed uterine serous carcinoma after RRSO during a follow up period lasting over 15 years (Shu et al., 2016). Uterine serous carcinoma accounts for approximately 10% of all uterine cancer cases in the general population. It is an aggressive disease process with a high rate of recurrence and accounts for up to 39% of uterine cancer mortality (Boruta et al., 2009). Hysterectomy at the time of RRSO could result in increased life expectancy (up to 5 months) and has been shown to be cost-effective in *BRCA1* carriers (Havrilesky et al., 2017). However, hysterectomy does not come without risks. When considering performing a hysterectomy, patients and providers must consider the additional risk incurred which include urinary tract injury, bowel injury, bleeding, pelvic pain, post-operative infection, and sexual dysfunction (Aarts et al., 2015).

In this study, we found an incidence of 2 uterine serous cancer cases among 258 *BRCA1* (0.8%) only carriers. This is comparable to the findings of the study by Shu et al. (Shu et al., 2016). One of these was diagnosed at the time of risk reducing surgery and the other many years later. The latter case could have possibly been prevented with hysterectomy at time of RRSO.

Limitations of this study include its cross-sectional nature, self-reported data, and potential for selection bias. There may have been patients who developed uterine cancer and died of their disease who would not be captured in this study. This study was targeted to respondents who have demonstrated an interest in *BRCA* topics as participants in the online social media group, which inherently implies that the respondents are a highly motivated and educated group and may be disproportionately so among all *BRCA* carriers. While most respondents were *BRCA* carriers, there were respondents who were *BRCA* negative or not tested as well. Major strengths of this study are its global

**Table 2**  
Decision for hysterectomy at time of risk reducing surgery by patient clinical characteristics among those who reported salpingo-oophorectomy.

Clinical and demographic characteristics	Did you have a hysterectomy (removal of uterus) at the time of your risk reducing salpingo-oophorectomy (removal of ovaries and fallopian tubes)?		P-value
	Yes (n = 189)	No (n = 150)	
Age at the time of survey	49.15 ± 9.22	47.15 ± 8.62	0.039*
Age at BRCA diagnosis	43.33 ± 8.83	41.96 ± 8.71	0.169
Gender, n (%)			0.195
Female	189/189 (100)	148/150 (98.7)	
Male	–	1/150 (0.7)	
Other	–	1/150 (0.7)	
Race, n (%)			0.560
White/Caucasian	174/189 (92.1)	139/150 (92.7)	
Multiple ethnicity/other	9/189 (4.8)	7/150 (4.7)	
Hispanic	3/189 (1.6)	2/150 (1.3)	
Black/African-American	–	2/150 (1.3)	
American Indian or Alaskan Native	2/189 (1.1)	–	
Asian/Pacific Islander	1/189 (0.5)	–	
Country, n (%)			0.1421
Canada	27/189 (14.3)	18/150 (12)	
Europe	15/189 (7.9)	18/150 (12)	
United States	135/189 (71.4)	96/150 (64)	
Other	12/189 (6.4)	18/150 (12)	
BRCA Status			0.076
BRCA1	94/189 (49.7)	70/149 (47)	
BRCA2	72/189 (38.1)	71/149 (47.7)	
BRCA1 and 2	–	1/149 (0.7)	
Variant of unknown significance	2/189 (1.1)	–	
Negative	9/189 (4.8)	1/149 (0.7)	
Not tested	6/189 (3.2)	4/149 (2.7)	
Other	6/189 (3.2)	2/149 (1.3)	

Mean ± SD.

% are expressed as column percentages.

applicability and number of patients surveyed. We were able to access a true international cohort of BRCA carriers with respondents from 19 nations across five continents.

Previous studies have described an association between uterine serous carcinomas and BRCA1 positive status. In this study, we found an incidence of 0.8% of uterine serous carcinoma among BRCA1 carriers. The rates of hysterectomy at the time of prophylactic surgery were high (> 50%) given that the incidence of uterine serous carcinoma after RRSO is much lower (< 5%). Further research needs to be conducted to explore the genetics of uterine cancers in BRCA patients and the lifetime risk of developing uterine cancer in these patients in order to determine whether hysterectomy should be recommended as part of the prophylactic surgery (Kwon et al., 2008).

**Conflict of interest**

None of the authors have any conflicts to report.

**Author contribution section**

Survey design: NN, ND, LG, LC.

IRB application and approval: NN, MS, LC.

Survey implementation: NN, ND, LG, LC.

Data analysis and review: NN, MS, ND, LG, SP, JO, LC.

Manuscript writing and editing: NN, MS, ND, LG, SP, JO, LC.

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