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Evaluation of screening and risk-reducing surgery for women followed in a high-risk breast/ovarian cancer clinic: it is all about the tubes in BRCA mutation carriers

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ABSTRACT

The objectives of this study were to determine both surgical and subsequent cancer outcomes for high-risk women from the University of Virginia's High-Risk Breast/Ovarian Cancer clinic undergoing ovarian cancer risk-reducing surgery. Retrospective review identified high risk women who had ovarian risk reducing surgery over the past decade and surgical outcomes, pathology, pre-operative screening results, and pre-/post-operative cancer diagnoses were evaluated. One hundred and eighty-three high-risk women had risk reducing surgery at a mean age of 50.1 years and with a mean BMI of 28.9 kg/m2 at the time of surgery. Most women (103; 56.3%) had a strong family history of cancer concerning for a hereditary syndrome without an identified mutation, 35.5% of women carried a known deleterious mutation and 7.7% of women had a personal history of breast or ovarian cancer. The most common procedure was a risk-reducing bilateral salpingo-oophorectomy with or without hysterectomy (RRBSO, 89.1%). All women underwent the Sectioning and Extensively Examining the Fimbriated End (SEE-FIM) pathology protocol which found two (1.1%) invasive ovarian cancers (one ovarian/tubal carcinosarcoma, one granulosa cell ovarian cancer), three (1.6%) serous tubal intraepithelial carcinomas (STIC), and one (1.1%) invasive fallopian tube cancer. Subsequent cancer diagnoses included one (0.5%) primary peritoneal cancer, four (2.2%) DCIS, and seven (3.8%) invasive breast cancers. Ultimately, among all high-risk women undergoing RR surgery, about 3.3% were diagnosed with a STIC or an ovarian cancer none of which were identified on screening. All STIC and tubal cancers were diagnosed in women with BRCA mutations (6.6% rate for this group).

1. Introduction

As a disease most often diagnosed in late stages following vague abdominal symptoms, ovarian cancer remains the leading cause of gynecologic cancer death and 14,070 women were expected to die of ovarian cancer in 2018 (Siegel et al., 2018). Up to 24% of women with ovarian cancer may harbor a deleterious germline mutation; the most common mutations are in the BRCA genes, but other genes are also associated with an increased risk of ovarian cancer including BRIP1, the Lynch associated genes, RAD51C, RAD51D, and STK11 (Pennington et al., 2014). Interestingly, patients with invasive epithelial ovarian cancer and a germline BRCA1/2 mutation tend to have a better prognosis than sporadically occurring ovarian cancers (Bolton et al., 2012).

Unlike breast cancer screening with mammograms and MRIs, the current ovarian cancer screening options of transvaginal ultrasound (TVUS) and Cancer Antigen 125 (Ca-125) have not proven effective in improving detection or survival in either the normal or high-risk population, as evidenced by the United Kingdom Trial of Ovarian Cancer Screening (UK-TOCS) and the United Kingdom Familial Ovarian Cancers Screening (UK-FOCS) trials (Rosenthal et al., 2017; Jacobs et al., 2016). Thus, in order to improve outcomes, current recommendations to enable ovarian cancer mortality reduction should focus on prevention and risk reduction, both surgical with risk-reducing bilateral salpingo-oophorectomy (RRBSO) and medical with oral contraceptives. In hereditary breast and ovarian cancer (HBOC) patients, the National Comprehensive Cancer Network (NCCN) guidelines recommend RRBSO by 35–40 years of age for BRCA1 carriers and by 40–45 years of age for BRCA2 carriers, which is much earlier than the

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Table 1
Demographics.

Characteristic	Known genetic mutation N (%) $N = 66$	No known genetic mutation N (%) $N = 117$	Total cohort N (%) $N = 183$
Mean age entered HR clinic (years)	48.32	49.67	49.18
Mean age at procedure (years)	49.06	50.68	50.1
Race			
Caucasian	57 (86.4)	101 (86.3)	159 (86.9)
African American	6 (9.1)	11 (9.4)	17 (9.3)
Hispanic	2 (3)	2 (1.7)	4 (2.2)
Asian	0 (0)	2 (1.7)	2 (1.1)
American Indian	1 (1.5)	1 (0.9)	2 (1.1)
BMI (kg/m^2)	28.43	29.15	28.89
Procedure Done			
BSO +/− hysterectomy[a]	65 (98.5)	98 (83.8)	163 (89.1)
USO (one ovary remaining)	1 (1.5)	7 (6.0)	8 (4.4)
Hysterectomy only (2 ovaries remaining)	0	3 (2.6)	3 (1.6)
Salpingectomy (2 ovaries remaining)	0	9 (7.0)	9 (4.9)
Reason for Surgery			
Known deleterious mutation	66	–	66 (35.9)
Family cancer history	–	103	104 (56.5)
Personal history of breast cancer	–	13	13 (7.1)
Personal history of ovarian cancer	–	1	1 (0.5)
Tube and Ovary Pathology			
Benign/no pathological abnormality	62 (94)	113 (96.6)	175 (95.6)
Atypia/malignancy	4 (6.1)	4 (3.4)	8 (4.4)
Procedure Costs (US Dollars)			
Hospital costs	$6907.03	$8081.32	$7637.17
Hospital charges	$23,283.70	$25,594.91	$24,691.52
Physician charges	$7605.97	$8117.02	$7592.98
Cancer following procedure			
None	56 (84.8)	115 (98.3)	171 (93.4)
DCIS	3 (4.5)	1 (0.9)	4 (2.2)
Breast cancer	6 (9.1)	1 (0.9)	7 (3.8)
Primary peritoneal adenocarcinoma	1 (1.5)	0	1 (0.5)

[a] 60 women underwent concomitant hysterectomy, the most common pathology was fibroids (34).

average age of menopause at 51 (National Comprehensive Cancer Network, n.d.). For high-risk patients with a known BRCA mutation, this procedure has been shown to reduce the risk of ovarian cancer by up to 80%, breast cancer by 50%, and all-cause mortality by 77% (Finch et al., 2014). For high-risk patients without an identified genetic mutation, a thorough family history and risk stratification can be performed to estimate their cancer risks and clinical judgment can be used to guide screening and preventive measures.

However, RRBSO does come with both economic and physiologic costs, including early menopausal symptoms, impaired sexual function, metabolic syndrome, heart disease, bone density loss, and surgical complications such as wound infection, bowel obstruction, or bladder perforation (Modesitt & Lu, 2017). The University of Virginia Health System opened a High-Risk Breast and Ovarian Clinic in 2007 to provide personalized cancer risk stratification, genetic counseling/testing, cancer screening, and prevention options for high-risk patients. The objectives of this study were to determine surgical outcomes, complications, and subsequent cancer outcomes for high-risk women undergoing ovarian cancer risk-reducing surgery at an academic tertiary care institution.

2. Material and methods

Following Institutional Review Board (IRB) approval, a retrospective chart review identified women who underwent an ovarian cancer risk-reducing surgery at the University of Virginia and were followed in the High-Risk Breast/Ovarian Cancer clinic since 2007. Patients followed in this clinic were deemed to be at high risk after their initial consultation if they carried a known genetic mutation, or met clinical criteria for a potential hereditary cancer syndrome, or had a first or second degree relative with ovarian cancer, or met the high risk breast criteria (over 20–25% lifetime risk of breast cancer). Data were abstracted from the electronic medical record and included patient demographics, medical and reproductive history, family cancer history, mutation status, surgery performed, pathology results, prior pelvic ultrasound results, Ca-125 levels, and pre-/post-operative cancer diagnoses. The Clinical Data Repository was also utilized to obtain total costs of the procedures done. Statistical analysis was conducted using IBM SPSS Statistics 24 (Armonk, NY). Independent T tests were used for continuous variables, and Chi-Square tests were used for categorical variables.

3. Results

One hundred and eighty-three high-risk women were identified with a mean age of 50.1 years and a mean BMI of 28.8 kg/m2 at the time of surgery (Table 1). Age at time of surgery did not differ between women with and without identified mutations. Most women underwent screening with either Ca-125 and/or transvaginal ultrasound (TVUS) prior to their surgery. The majority (103; 56.2%) had strong family history of cancer consistent with a hereditary syndrome, or an ovarian cancer family history, or personal history of early breast/ovarian cancer without an identified mutation (14;7.7%). The remaining women carried a deleterious mutation in BRCA2 (33; 18.0%), BRCA1 (28; 15.3%), Lynch mutations (4; 2.2%) or p53 (1; 0.5%). The most common procedure performed was a RRBSO (89.1%) with or without a hysterectomy (32.8 and 56.2% respectively), followed by USO (4.4%), bilateral salpingectomy (4.9%) and hysterectomy/bilateral salpingectomy (1.6%). The vast majority of surgery (78%) was performed for risk reduction vs. 14.5% for symptoms and 7% due to abnormal screening. No ovarian or fallopian tube cancers were detected on screening. Mean surgical hospital costs, hospital charges, and physician charges were $7637.17, $24,691.52, and $7592.98 respectively for the surgical procedures. There were no major surgical complications, readmissions, or mortalities.

All women underwent the Sectioning and Extensively Examining

Table 2
Demographics with pathology outcomes ($N = 184$).

Factors	Cancer/Atypia $N = 8$	Benign $N = 175$	*P*-Value
Age at Surgery (years)	52.6	49.98	0.445
BMI (kg/m^2)	25.3	29.1	0.129
Race			0.932
Caucasian	8	150	
African American	0	17	
Hispanic	0	4	
Asian	0	2	
American Indian	0	2	
CA-125			0.627
Normal (≤30)	6	127	
Elevated (> 30)	0	5	
Not performed	2	43	
Mean CA-125	15.17	11.99	0.570
Pelvic US			0.663
Normal	1	46	
Abnormal – benign	3	69	
Abnormal – requires intervention	1[a]	13	
Not performed	3	46	
Mutation Status			0.404
Known deleterious mutation	4	62	
BRCA1	2	26	
BRCA2	2	31	
MSH2	0	2	
MSH6	0	1	
PMS2	0	1	
P53	0	1	
No known mutation	4	113	
Cancer diagnoses following procedure			0.592
None	7	164	
Breast cancer	1	6	
DCIS	0	4	
Primary peritoneal serous adenocarcinoma	0	1	

[a] Ultrasound abnormality was on opposite side of the microscopic atypia that was found.

the Fimbriated End (SEE-FIM) protocol with extensive pathologic analysis which found two (1.1%) invasive ovarian cancers (one carcinosarcoma of ovary/tube, one granulosa cell), three (1.6%) serous tubal intraepithelial carcinomas (STIC), and one invasive fallopian tube cancer (0.5%). All tubal pathology was diagnosed in women with documented BRCA mutations. There were no statistically significant differences in age at procedure, Ca-125 levels, TVUS results, mutation status, or subsequent cancers between patients in which atypia or cancer was found on pathology compared to benign pathology (Table 2). A clinical summary of the eight patients with abnormal pathology at the time of risk-reducing procedure can be found in Table 3.

Of the 175 patients with normal/benign pathology at the time of RRBSO, 12 patients were diagnosed with subsequent cancers (Breast-7, DCIS-4, Primary Peritoneal-1, Table 4). Of note, the majority of women with subsequent cancers (7/12; 58.3%) carried BRCA 1 mutations, which represents 25% of the BRCA 1 mutation carriers within the cohort (7/28). The woman diagnosed with primary peritoneal cancer was 6 years out from her RRBSO (with benign RRBSO pathology and cytologic washings) and 9 years out from her prior breast cancer diagnosis. The peritoneal adenocarcinoma was discovered following a markedly elevated Ca-125 (606) and confirmed on laparoscopy with subsequent debulking and omentectomy/hysterectomy but with essentially only extensive miliary disease.

4. Discussion

Unfortunately, current ovarian cancer screening modalities with ultrasound and Ca-125 appear to be ineffective, perhaps influenced by the fact that the majority of serous epithelial cancers likely originate in the fallopian tubes (Perets & Drapkin, 2016). Cells from the fimbriae of fallopian tubes lie in close proximity to the ovaries, and cells may slough off and attach to the epithelial surface of the ovary. Presumed epithelial ovarian and fallopian tube cancers appear histologically identical and their clinical behavior is also indistinguishable. As RRBSO use has increased, it has been shown that up to 5.4% of asymptomatic BRCA1/2 carriers have occult carcinomas at the time of surgery and most occult cancers are found in the fallopian tube, similar to our study's findings (Zakhour et al., 2016). The presumed precursor lesion, known as a STIC, was incidentally found in three subjects, all of whom carried BRCA mutations for an overall STIC rate of 3/61 (4.9%) for BRCA mutation carriers and 0% for wildtype-BRCA patients.

A key to developing a more effective screening method is discovering the lead time to developing a STIC as well as the time from STIC development to an invasive cancer as those are the times when more targeted interventions could be implemented. The time from STIC to invasive cancer has been suggested to be approximately 7 years and has guided the recommendation for RRBSO at 35–40 years of age in BRCA1 patients (Labidi-Galy et al., 2017). Our study included only one patient outcome to potentially support this timeline, the BRCA1 patient who developed primary peritoneal cancer 6 years after having a RRBSO (at a much later than recommended 48 years of age) with close sectioning and normal pathology. Presumably the fallopian tube epithelial

Table 3
Abnormal pathology cases at RRBSO.

Case	Mutation	Procedure done	Age at procedure	RRBSO pathology	Cancer before procedure	Cancer after procedure
1	None	Hyst/BSO	42	Ovary – Adult granulosa cell tumor Tubes – NPA	None	None
2	None	Hyst/BSO	43	Ovary – Hemorrhagic and follicle cysts Tubes – Epithelial Atypia	None	None
3	None	Hyst/BSO	56	Ovary – Malignant muellerian mixed tumor Tubes – Malignant muellerian mixed tumor	None	None
4	None	BSO	66	Ovary – Leydig cell hyperplasia, rete ovarii Tubes – Epithelial atypia & tubal endometriosis	Basal cell and squamous cell carcinoma of the skin	None
5	BRCA1	Hyst/BSO	45	Ovary – Fibroma & cortical inclusion cysts Tubes – STIC	None	None
6	BRCA1	Hyst/BSO	59	Ovary – Serous cystadenoma with focal cytologic atypia & benign mesothelial-lined cyst Tubes – NPA	Breast Cancer	Breast Cancer
7	BRCA2	BSO	44	Ovary – NPA Tubes – STIC	None	None
8	BRCA2	BSO	66	Ovary – NPA Tubes – Stage I_A Fallopian Tube Cancer and STIC	Squamous cell carcinoma of the tongue	None

Hyst/BSO = hysterectomy and bilateral salpingo-ophorectomy; NPA = no pathologic abnormality; STIC = serous tubal intraepithelial cancer.

Table 4
Subsequent cancer diagnoses among women undergoing ovarian risk reducing surgery.

Case	Mutation	Procedure done	Age	Pathology from RRBSO	Cancer before procedure	Cancer after procedure
9	None	USO + US	47	Ovary – serous cystadenoma Tubes – NPA	None	DCIS
10	None	Hyst/BSO	62	Ovary – simple cyst Tube – NPA	DCIS and endometrial cancer	Breast cancer
11	BRCA1	BSO	48	Ovary – NPA Tubes – NPA	Breast cancer	Primary peritoneal cancer 6 years later
12	BRCA1	BSO	57	Ovary – endosalpingiosis and suture granuloma Tubes – NPA	Breast cancer x2	DCIS
13	BRCA1	BSO	52	NPA	None	DCIS
14	BRCA1	BSO	58	NPA	None	Breast Cancer
15	BRCA1	Hyst/BSO	32	Ovary – NPA Tube – fibrous adhesions	Breast cancer	Breast Cancer
16	BRCA1	BSO	48	Ovary – “pelvic floater” calcified stromal tissue Tube – NPA	Breast cancer	Breast Cancer
17	BRCA1	Hyst/BSO	59	Ovary – serous cystadenoma with focal cytologic atypia Tube – NPA	Breast cancer	Breast Cancer
18	BRCA2	BSO	55	NPA	None	DCIS
19	BRCA2	BSO	56	Ovary – follicle cyst Tube – simple paratubal cyst	Breast cancer	Breast Cancer
20	BRCA2	BSO	35	Ovary – simple cyst Tube – simple paratubal cyst	Breast cancer	Breast Cancer

BSO = bilateral salpingo-oophorectomy; Hyst = hysterectomy; DCIS = ductal carcinoma in situ (breast cancer precursor); NPA = no pathologic abnormality.

cells were exfoliated or remained following the RRBSO procedure or the cancer developed de novo in the peritoneum. It has been suggested that including peritoneal washings at the time of RRBSO (done routinely as part of our practice) may aid in detection of abnormal cytology and guide staging for those found with early invasive or in-situ pathology, but this patient did have negative cytology at original RRBSO (Manchanda et al., 2012).

With ineffective current screening, removal of both ovaries and fallopian tubes remains the best method of reducing the risk of developing ovarian cancer in high-risk women. These procedures come with financial, physical, and psychological costs to the patient, primarily due to the premature loss of the ovarian hormones, perhaps explaining the later age at time of surgery within our cohort which had more high-risk women without a defined mutation. The average financial costs of RRBSO in our cohort, as expected, are lower than the average cost for ovarian cancer treatment, estimated by one institution to average $211,940 per patient (Louis et al., 2009), and a pre-emptive surgery results in improved survival and decreased costs for patients and society.

Ongoing studies investigating the efficacy of salpingectomy (rather than RRSO) will hopefully help to answer the questions about the efficacy and safety of this intervention that could reduce the consequences of premature ovarian removal. This strategy of both opportunistic salpingectomy in normal risk women as well as staged salpingectomy followed by oophorectomy at a later time point to preserve hormonal function in high risk women is currently gaining traction and is under study. Two potential safety concerns for this strategy are that not all ovarian cancers arise in the fallopian tube and also, a recent study found that fimbrial tissue may actually remain on the ovaries following a salpingectomy in 16% of patients with unclear clinical significance (Gan et al., 2017). In our study, the one epithelial fallopian tube cancer was found in a BRCA carrier who was found to have the deleterious mutation at a very late (age 65) and thus her surgery was performed 20 years later than would be recommended for that population.

Nearly all of the women in our study had risk-reducing surgeries at an age much later than recommended, possibly due to personal risk/benefit analysis, insurance coverage of surgeries especially in women lacking a defined mutation, or lack of clarity about cancer risk and optimal timing. It is imperative that high-risk women are identified by their physicians and referred to specialized cancer or genetic specialist centers so as to have access to this lifesaving intervention, if appropriate. A recent study of a community OB/GYN practice demonstrated that 23.8% of women met NCCN criteria guidelines for genetic testing due to high risk of hereditary cancer (DeFrancesco et al., 2018). Warning signs prompting referral for further high-risk evaluation for potential ovarian cancer risk include personal or family history of cancers associated with genetic syndromes such ovarian cancer, breast cancer, pancreatic cancer, male breast cancer, and endometrial or colon cancer. Multiple family members are often affected and at an earlier age than most sporadic malignancies. Continuing to educate primary care physicians as well as practicing OB/GYN's to recognize these hereditary flags is imperative. Of note, the women followed in this study had surgeries prior to the stronger recommendation of hysterectomy in BRCA1 patients for endometrial cancer risk reduction, and most hysterectomies done in this study were simply based on patient/physician preference or other indications for a hysterectomy(e.g. fibroids).

Consideration of the effects of ovaries in the development of breast cancer in patients with BRCA mutations must also be taken into account. Of the BRCA1/2 patients in our study, 16.4% (10/61) developed subsequent related cancers (DCIS, breast, and peritoneal cancer), in contrast to 1.6% (2/122) of patients without a confirmed BRCA1/2 mutation. This is especially relevant for patients with BRCA2 mutations, in whom breast cancer is often estrogen receptor positive and thus susceptible to continued production of estrogen by remaining ovaries.

In conclusion, germline BRCA germline mutations impart greatly increased risk for the development of ovarian cancer, which is often derived from fallopian tube epithelium rather than purely the ovaries themselves. In order to truly decrease ovarian cancer mortality, there must be a renewed focus on identifying such high-risk patients to allow for the option of a RRBSO well prior to the potential onset of a likely fatal cancer.

Conflicts of interest

The authors report no conflicts of interest.

Author contributions

Susan C. Modesitt, Martha E. Stewart, Anne T. Knisely, Mackenzie W. Sullivan, and Kari L. Ring all contributed fully to the planning, writing, and submission of this article.

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Disclosures

None.

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