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Occult ovarian cancers identified at risk-reducing salpingo-oophorectomy in a prospective cohort of *BRCA1/2* mutation carriers

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This study is conducted for the PROSE Consortium. The details of the PROSE Consortium are listed in Appendix.

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Abstract

Risk-reducing salpingo-oophorectomy (RRSO) is widely used for cancer risk reduction in *BRCA1* or *BRCA2* (*BRCA1/2*) mutation carriers. Occult ovarian/fallopian tube cancers (OOC) detected at the time of RRSO have been reported in several studies with wide variability in reported prevalence. We estimated the prevalence of OOC in a prospective cohort of 647 *BRCA1/2* mutation carriers from 18 centers (PROSE consortium) who under-went RRSO between 2001 and 2008. OOC was detected in 16 of 647 women (2.5%). The mean age at RRSO was 51.7 in those with OOC versus 46.6 in those without OOC ($P = 0.017$). Twelve of the 16 OOCs (75%) were diagnosed in women with *BRCA1* mutations. Thirty-eight percent of women with OOC had stage 1 cancer versus none of the women in the PROSE database diagnosed with ovarian cancer outside of screening. Among 385 women (60%) in whom pathology reports were available for central review, 246 (64%) RRSOs were performed at participating PROSE centers while 139 (36%) were performed at local sites. Ovarian and fallopian tube tissues removed at major genetics referral centers were significantly more likely to have been examined in toto compared to specimens obtained at non-referral centers (75% vs. 30%, $P < 0.001$). Our results confirm that OOC may be found at the time of RRSO in *BRCA1/2* mutation carriers and suggest that OOC are of a more favorable stage than cancers found outside RRSO. An unacceptably high proportion of pathologic examinations did not adequately examine ovaries and fallopian tubes obtained at RRSO.

Keywords

Hereditary ovarian cancer; Prophylactic Surgery; *BRCA1*; *BRCA2*

Introduction

Women with inherited *BRCA1* or *BRCA2* (*BRCA1/2*) mutations are recommended to undergo risk-reducing salpingo-oophorectomy bilateral prophylactic oophorectomy(RRSO) to reduce their cancer risk, generally by age 40 or after the completion of childbearing [1,2]. In

BRCA1/2 mutation carriers, RRSO reduces the risk of ovarian cancer by approximately 85–90% and the risk of breast cancer by 50% or more [3], and may also impact cancer-specific and overall mortality [4]. These numbers also reflect the fact that cancer risk reduction associated with RRSO is not complete, and that residual risk may exist for peritoneal cancers even after RRSO. Furthermore, women who undergo RRSO undergo premature menopause, which may confer risk for complications such as hot flashes, osteopenia, and heart disease [5]. While there is some evidence that short-term use of hormone replacement therapy after RRSO does not negate the reduction in breast cancer risk conferred by RRSO [6,7] careful consideration of the timing and risks versus benefits of RRSO need to be considered prior to surgery in women with *BRCA1/2* mutations who are deciding on their options for cancer prevention.

Occult ovarian and fallopian tube cancers (OOC) have been reported at the time of RRSO (reviewed in [8]). The prevalence of OOC has been estimated to be 2.3–23.5% [9-15]. At the low end of this range, OOC prevalence may in part reflect missed ovarian tumors if pathological examination of surgical specimens was incomplete or the sample involved women who were relatively young in age. At the high end of this range, these figures may represent extensive pathologic review, biases due to sample selection, or have involved women who were relatively older in age. In order to clarify the prevalence and characteristics of OOC, we undertook a multicenter prospective cohort study of 647 women who underwent RRSO after disclosure of a positive *BRCA1/2* mutation result.

Methods

Participants and data

Women with germline, disease-associated *BRCA1/2* mutations were identified from 18 North American and European centers that comprise the PROSE consortium: University of Vienna, Austria; Baylor University, Beth Israel; Evanston Northwestern; Mayo Clinic; Creighton University, Omaha, NE; Dana-Farber Cancer Institute, Boston, MA; Fox Chase Cancer Center, Philadelphia, PA; Georgetown University, Washington, DC; University of Chicago, Chicago, IL; University of Pennsylvania, Philadelphia, PA; Netherlands Cancer Institute, Amsterdam, Netherlands; Royal Marsden Hospital, Sutton, UK; St. Mary's Hospital, Manchester, UK; Guys Hospital, London, UK; University of Texas; Yale University, New Haven, CT; and Baylor-Charles A. Sammons Cancer Center, Dallas, TX. The *BRCA1/2* mutation status of all participants was confirmed by direct mutation testing with full informed consent under protocols approved by the human subjects review boards at each institution. Women with *BRCA1/2* variants of unknown functional significance were excluded.

All participants were identified via genetic testing and counseling programs for clinical and research purposes. Participants were referred by clinicians or relatives because they were perceived to be at risk for hereditary breast and/or ovarian cancer. Genetic counseling and testing was performed under clinical and/or research protocols specific to the IRB guidelines of each center. Follow-up from the time of a positive genetic test result was conducted within each center on a periodic basis. This follow-up was active but did not occur at equal intervals for all individuals in this multicenter observational study. Follow-up was random with respect to RRSO use, cancer occurrence, or death. In addition, because this was not a randomized clinical trial of RRSO, both the case and the control groups underwent a variety of cancer surveillance programs that were not controlled for in this study.

Study participants were enrolled as a prospective cohort to avoid potential biases inherent to multicenter referral studies of this type [16,17]. Participants were defined as women with a deleterious *BRCA1* or *BRCA2* mutation. Women with a mutation in both *BRCA1* and *BRCA2*, or with a variant of unknown significance, were excluded. Women were eligible if

they had a genetic test disclosure date and had at least one ovary intact at the time of genetic test disclosure. For our primary analysis, we estimated the prevalence of OOC found at time of RRSO. All women in the primary analysis underwent a RRSO during the period 2001–2008 and after disclosure of their positive genetic test result. We limited the range of RRSO dates to this period to better reflect current trends in medical practice. In addition, we studied women who underwent RRSO but were not found to have any malignancy at the time of their RRSO, and we studied women who did not undergo RRSO but were diagnosed with ovarian cancer after the disclosure of their positive genetic test result (ovarian cancer cases).

Entry and follow-up of study participants at each center were undertaken without regard to surgical status. Overall research participation for potentially eligible women varied by study center from 80 to 100%, with a mean overall participation rate of 90.2%. Vital status and cancer history were obtained on all eligible participants using medical records, telephone interviews, and/or self-administered questionnaires. Reproductive and exposure history, including hormone use and smoking, were obtained by a baseline questionnaire near the time of enrollment. Follow-up data on RRSO, cancer diagnoses, and deaths were verified by review of medical records, operative notes, and/or pathology reports. Specific information collected regarding prophylactic surgeries included type of ovarian surgery and reason for surgery. Pathology data were collected at each center. Pathology reports were re-reviewed at the University of Pennsylvania. Reports were specifically examined for phrases such as “representative sections submitted” versus “entirely submitted” or “submitted in toto” to determine the extent of histologic examination.

Statistical analysis

Descriptive comparison of occult cancer and non-occult cancer controls was performed using Fisher’s Exact Test (for discrete variables) or *t*-test (for continuous variables). All analyses were undertaken using STATA9.1 (College Station, TX).

Results

Among 647 women who underwent RRSO after disclosure of a positive genetic test for *BRCA1/2* mutations OOC was diagnosed in 16 (2.5%). Characteristics of women in our sample are shown in Table 1. No differences in year of RRSO, pre-RRSO breast cancer status, nulliparity, number of live births, or percentage of *BRCA1* versus *BRCA2* mutation carriers were seen between those with or without OOC at the time of RRSO. However, compared to controls (those without OOC at RRSO), those with OOC were less likely to have ever used oral contraceptives ($P = 0.046$), particularly in the *BRCA2* mutation carrier group ($P = 0.039$). In addition, *BRCA1* mutation carriers with OOC were more likely to smoke compared to those without OOC ($P = 0.036$). Those who were found to have OOC at RRSO were born earlier than those without OOC. The mean age at RRSO among women with OOC was 51.7 years compared to 46.6 years in women without OOC ($P = 0.017$). When stratified by gene, these differences were accounted for by women with *BRCA2* mutations, with a mean age at RRSO of women with OOC of 62.4 years compared to 48.4 years in women without OOC ($P = 0.001$).

Three of the 16 (18.8%) OOC were primary Fallopian tube cancers. Twelve of the 16 (75%) OOCs were diagnosed in women with a *BRCA1* mutation. Two women with a *BRCA1* mutation were diagnosed with OOC under the age of 40. Neither of these women had been diagnosed with breast cancer, both had a bilateral salpingo-oophorectomy with hysterectomy. The first woman had a C61G mutation in *BRCA1*, and was diagnosed with a stage 2 papillary serous carcinoma at age 35.6. The second woman, with an ex1A-2 mutation (a large genomic deletion found on MLPA with absence of exon 1a and exon 2) in *BRCA1*, was diagnosed with a stage 1 serous carcinoma at age 38.8. Four OOC were diagnosed in *BRCA2* mutation carriers, none of these were diagnosed prior to age 40.

We detected a possible temporal trend in the diagnosis of OOC in our sample set. While the primary analysis used here included only women who had undergone RRSO in 2001–2008, the prevalence of OOC in a similarly defined prospective cohort of women undergoing RRSO prior to 2001 was lower, with 2 of 253 (0.8%) procedures done prior to 2001 resulting in OOC compared with 16 of 647 (2.5%) procedures performed from 2001 to 2008 ($P = 0.119$).

We also compared OOC to ovarian cancer not detected incidentally at the time of RRSO. The characteristics of the two groups were similar: there were no statistically significant differences in year of surgery, smoking, oral contraceptive use, breast cancer status, number of live births, percent with children, percentage of *BRCA1* versus *BRCA2* carriers, or year of birth. However, more OOC were diagnosed at earlier stage than were ovarian cancers found outside the context of RRSO (Table 2). Six of 16 (37.5%) OOC were stage I at diagnosis, compared to none of 16 non-occult ovarian cancers ($P = 0.023$; corrected two-sided χ^2). One non-occult ovarian cancer was detected under age 40 in a *BRCA1* carrier. The mean follow-up time from genetic testing to OOC or ovarian cancer diagnosis was 1.15 years. The median follow-up from diagnosis of OOC was 1.94 years, and from ovarian cancer diagnosis was 2.87 years. At the end of follow-up, 15 (94%) of women with OOC were alive. One of the 16 (6.3%) OOC cases had died of ovarian cancer. In comparison, 14 of the 16 non-occult cancer group were still alive at follow-up, while two (12.5%) had died from ovarian cancer (Fisher's exact test *P*-value = 0.999).

Pathology reports were obtained and centrally reviewed for 385 RRSO surgeries (60%). 167 of 385 (43%) RRSOs underwent concomitant hysterectomy. 245 (63.6%) of these RRSOs were performed at a participating PROSE referral center or a closely affiliated hospital, whereas 140 (36.4%) were performed at non-tertiary care centers or community hospitals. In 226 of 385 RRSOs (58.7%), ovaries and fallopian tubes were specifically stated on the pathology report to have been examined in toto. In 32 (8.3%) cases, the ovaries were examined in toto, but the fallopian tubes were not. In the remaining 127 (33.0%) RRSOs, neither ovaries nor fallopian tubes were identified as having been examined in toto. Specimens obtained at surgery at a major genetics referral center were significantly more likely to have been examined in toto compared to specimens obtained at local sites (75 vs. 30%, $P < 0.001$). There was no difference in the frequency of detection of occult malignancies at genetics referral centers compared with non-referral centers (3.7 vs. 4.3%, $P = 0.789$).

In addition to the 647 women were included in this analysis, three additional women from the PROSE cohort underwent RRSO following receipt of their genetic test results with negative pathology at the time of surgery but have subsequently developed primary peritoneal cancer. These women were excluded as controls (i.e., non-OOC) for the primary endpoint of prevalence of OOC, given the possibility that they may have had OOC at the time of their initial surgery. The inclusion of these three in the control group did not change the results (data not shown); if included as cases, the prevalence of OOC becomes 2.9%. Patient 1 underwent TAH/BSO at age 36 at a major genetics center and her ovaries were examined in toto but the fallopian tubes were not recorded as fully examined; she developed primary peritoneal cancer at age 37. Patient 2 underwent TAH/BSO at age 47 at a local center but there is no documentation that ovaries or fallopian tubes were examined in toto; she developed primary peritoneal cancer at age 52. For Patient 3, initial pathology of RRSO at age 52 was not available, and she developed primary peritoneal cancer at age 56. Mean time from RRSO to primary peritoneal cancer in these three women was 2.37 years. All three women prospectively diagnosed with primary peritoneal cancer were *BRCA1* mutation carriers.

Discussion

We report that OOC is detected in less than 3% of women with *BRCA1/2* mutations who are undergoing RRSO, and that the tumors detected at the time of surgery are of a more favorable stage than those detected outside of prophylactic surgery.

A number of previous reports have estimated the prevalence of OOC in *BRCA1/2* mutation carriers. These range from 2–3% in the larger multicenter series [10,12,13,18] to 8–24% in smaller, generally single institution series with more extensive pathologic review [9,11,14, 19-22]. The lower estimates may in part reflect missed ovarian tumors if pathological examination of surgical specimens was incomplete or the sample involved women who were relatively young in age. Most studies with higher estimates have performed extensive pathologic review with specific attention to full sectioning of the ovaries and fallopian tubes. Such studies suggest that there may be an underestimate of OOC in the absence of complete pathologic review, particularly of the fallopian tube. Powell et al. [21] have reported a rigorous post-RRSO pathologic assessment including cytology of peritoneal washings, serial sectioning of ovaries and fallopian tubes, as well as peritoneal and omental biopsies. In 67 procedures, 7 (10.4%) occult malignancies were found in the ovaries and fallopian tubes. In second study, 6 of 62 (9.7%) women with *BRCA1* or *BRCA2* mutations were found to have occult neoplasia at the time of RRSO following a standard surgical and pathologic protocol that included serial sectioning of the fallopian tubes and ovaries [19]. In addition to OOC, high rates of premalignant histology have also been reported among high-risk women undergoing RRSO [23]. Therefore, the lower prevalence estimates from this study for OOC may reflect suboptimal histologic examination of the ovaries and fallopian tubes.

The data we present provide additional support for the observation seen in prior studies that there may be inadequate evaluation of surgically removed tissue in some settings. Our data show that complete histologic examination only occurred in 60% of the cases studied. When RRSO was performed at PROSE centers (i.e., specialized referral centers), the rate of complete histologic examination was significantly higher than in non-PROSE center (e.g., community hospitals). Inadequate histological evaluation may lead to failure to detect and appropriately manage occult ovarian cancer (i.e., inappropriate treatment of a primary cancer), which in turn could lead to post-RRSO peritoneal cancer and unfavorable clinical outcomes. However, in this study, only three primary peritoneal cancers were identified of which two had pathology reports available for review. In neither was there documentation of full sectioning of both the ovaries and fallopian tubes. Therefore, we do not have sufficient evidence at this time to conclude that inadequate pathologic examination increases the risk of a subsequent primary peritoneal diagnosis.

Primary peritoneal cancer has been reported in women with *BRCA1/2* mutations following RRSO with an estimated frequency of 2–5%, and may occur more frequently in *BRCA1* compared to *BRCA2* carriers [12,13,24]. However, the proportion of these post-RRSO cancers that may represent relapses from an occult neoplasm remains to be determined. In studies that have examined this question, “full” pathologic examination may be associated with a very low risk of subsequent peritoneal cancer compared to those undergoing “standard” pathologic examination [19] or in those cases where salpingectomy was not performed [14,21,25]. The lack of intensive pathology evaluation at the time of RRSO may impact estimates of post-RRSO primary peritoneal cancer rates: if occult malignancies are missed at the time of surgery, some of these will relapse and be considered a failure of RRSO, when in fact timely diagnosis and adequate treatment could significantly improve outcome.

The importance of the fallopian tube in relationship to ovarian cancer, both in *BRCA1* and *BRCA2* mutation carriers and in sporadic cancers has been increasingly recognized [26,27].

Callahan et al. [26] studied 122 *BRCA1/2* mutation carriers who were undergoing RRSO at a median age of 46.5 years. They reported that 7 of these women (5.7%) had an early malignancy that originated in the fimbria or ampullary region of the fallopian tube. These data suggest that fallopian tube malignancies may represent an important site of origin of tumors detected at the time of RRSO. Three of the 16 (18.8%) OOC in our series originated in the fallopian tube.

Our findings support the current recommendations that that ovarian and fallopian tube tissue be removed as completely as possible and be examined in toto [28] (Table 3). However, the role of peritoneal washing or random peritoneal biopsies is uncertain. In Powell et al. [21], undertook intense histologic examination, and all OOC were detected on serial sectioning, none by peritoneal biopsy or washings alone. Eitan et al. [29] reported that 11% of 117 women who underwent peritoneal washings at the time of RRSO had mesothelial atypia, but none had developed peritoneal cancer at a median follow-up of 20 months. Agoff et al. [30] described two patients with abnormal peritoneal washings, but both had fallopian tube cancers on examination. At the current time, it is not clear that peritoneal washings add to complete examination of the ovaries and fallopian tubes.

The role of hysterectomy at the time of RRSO is also unclear but not routinely recommended [31]. Hysterectomy may simplify hormone replacement therapy for those women who choose to take it, but its role in further reducing ovarian/fallopian cancer risk by removing the small remnant of fallopian tube left attached to the uterine wall at the time of RRSO is unknown. Two of the three women in this series who developed primary peritoneal cancer had undergone hysterectomy at the time of their RRSO.

A number of other factors, including age, may affect the prevalence of OOC. Although not statistically significant in this study, more *BRCA1* mutation carriers (3.2%) were found to have OOC compared to *BRCA2* mutation carriers (1.5%), despite a later age of oophorectomy in the latter group. These data support previous findings of an increased risk of occult ovarian cancers in *BRCA1* (6.4%) compared to *BRCA2* (1.5%) mutation carriers [13,19]. In our study, only two OOC were observed out of 134 (1.5%) women who underwent RRSO under age 40; compared to 14 of 513 (2.7%) 40 and older. There have been several reports suggesting that later age of RRSO significantly increases the risk of OOC. In a series of 113 high risk women, Lamb et al. [19] reported that the risk of occult neoplasia was 18.8% in *BRCA1/2* mutation carriers undergoing RRSO after age 45, while others have demonstrated that older age is a significant risk factor for premalignant or malignant lesions [13,21].

The presence of OOC in approximately 3% of *BRCA1* carriers allows an estimate of lead time and a potential “window” for early identification in surveillance. Given an annual incidence of ovarian cancer around 1% in *BRCA1* carriers aged 40–79 years [32,33], and the fact that most ovarian cancers diagnosed during screening are of later stage [34], this suggests a period of about 2 years prior to symptomatic (generally stage III/IV) disease during which early diagnosis is likely to improve survival.

There are several imitations of this study. Not all pathology reports relating to RRSO were available for review. We performed a central review of available pathology reports, but not of pathology slides. Therefore, it is possible that some of specimens were examined in toto, even if they were not reported as such. However, an argument can be made that reporting should be unambiguous to the physicians taking care of women with *BRCA1/2* mutations. In addition, the reason that the specimens were not processed in toto may be because the pathologists did not have all the clinical information available at the time of pathology review. At times, patients and providers have been reluctant to include *BRCA1* and *BRCA2* mutation status in the medical record. Given the importance of this information to the reviewing pathologist, and in light of protections afforded by the Genetic Information Non-Discrimination Act, we strongly

encourage that *BRCA1/2* status be made available to all care providers of women with these mutations. Finally, despite the large consortium and relatively large number of prospectively followed mutation carriers, there remain limited numbers of post-RRSO primary peritoneal cancer diagnoses in our study sample. Therefore, we are unable to link the absence of pathologic review to clinical outcomes.

In summary, OOC in *BRCA1/2* mutation carriers occur. Unfortunately, many women undergoing RRSO in this prospective study did not have what is now considered standard pathologic assessment of the ovaries and fallopian tubes. Women undergoing RRSO should have salpingo-oophorectomy, and their ovaries and fallopian tubes should be examined in toto. Continued follow-up of large samples of women with *BRCA1/2* mutations who have had RRSO are needed to determine whether any predictors of post-RRSO primary peritoneal cancer can be identified.

Appendix

The PROSE Consortium includes the following centers and individuals: Baylor-Charles A. Sammons Cancer Center (Joanne L. Blum, M.D. Ph.D., Becky Althaus, R.N., C.G.C., Gaby Ethington), Baylor College of Medicine (Sharon Plon, M.D., Ph.D., Claire Noll), Beth Israel Deaconess Medical Center (Nadine Tung, M.D.), City of Hope National Medical Center (Jeffery Weitzel, M.D., Veronica Lagos), Creighton University (Henry T. Lynch, M.D., Patrice Watson, Ph.D., Carrie Snyder, B.A.,), Dana Farber Cancer Institute (Judy E. Garber, M.D., M.P.H., Katherine Corso, Kathryn Stoeckert), Duke University (Joellen Schildkraut, Ph.D.), Northshore University Health System (Wendy Rubinstein, M.D., Tina Selkirk), Fox Chase Cancer Center (Mary B. Daly, M.D., Ph.D., Irene Angel), Georgetown University (Claudine Isaacs, M.D., Grace Zawistowski,), Guys and St. Thomas Foundation Trust (Gabriella Pichert, M.D., Caroline Langman, Leena Gohil) Jonsson Comprehensive Cancer Center at the University of California, Los Angeles (Patricia A. Ganz, M.D., Joyce Seldon), Mayo Clinic College of Medicine (Fergus Couch, Ph.D.), Netherlands Cancer Institute (Marc van Beurden M.D., Ph.D., Laura van ‘t Veer, Ph.D.), Royal Marsden Hospital (Rosalind Eeles, M.D., Elizabeth Bancroft), St. Mary’s Hospital (Gareth Evans, M.D., Andrew Shenton), University of Chicago (Shelly Cummings, Olufunmilayo Olopade, M.D.), University of California, Irvine (Susan L. Neuhausen, Ph.D., Linda Steele), University of Pennsylvania (Susan Domchek, M.D., Tara Friebel, M.P.H., Timothy Rebbeck, Ph.D.), University of Texas, Southwestern (Gail Tomlinson, M.D.), University of Vienna (Christian F. Singer, Georg Pfeiler), Women’s College Hospital (Steven A. Narod, M.D.), Yale University (Ellen Matloff, M.S., Karina Brierly).

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Table 1

Characteristics of women with a RRSO performed 2001–2008 after disclosure of a positive *BRCA1/2* test

Variable	Total sample			*BRCA1*			*BRCA2*		
	OOC (*N* = 16)	No ovarian cancer (*N* = 631)	*P*-value	OOC (*N* = 12)	No ovarian cancer (*N* = 376)	*P*-value	OOC (*N* = 4)	No ovarian cancer (*N* = 255)	*P*-value
Mean birth year (range)	1951 (1928–1967)	1957 (1927–1978)	0.007	1955 (1944–1967)	1958 (1927–1978)	0.175	1941 (1928–1949)	1955 (1929–1971)	0.001
Mean age at RRSO, years (range)	51.7 (35.6–76.4)	46.6 (25.8–75.3)	0.017	48.1 (35.6–60.4)	45.4 (25.8-75.3)	0.249	62.4 (56.1–76.4)	48.4 (33.1–72.9)	0.001
Mean RRSO year (range)	2003 (2001–2005)	2003 (2001–2008)	0.231	2003 (2001–2005)	2003 (2001–2007)	0.433	2003 (2001–2005)	2004 (2001–2008)	0.393
Parous (%)	11 (69%)	413 (78%)	0.378	7 (58%)	244 (78%)	0.156	4 (100%)	169 (77%)	0.577
Mean number of live births (range)	2.1 (2–3)	2.5 (2–8)	0.094	2.1 (2–3)	2.5 (2–5)	0.226	2 (2–2)	2.5 (2–8)	0.244
Ever user of oral contraceptives (%)	9 (60%)	466 (82%)	0.046	8 (73%)	283 (84%)	0.395	1 (25%)	183 (78%)	0.039
Ever smoker (%)	9 (60%)	246 (42%)	0.190	9 (75%)	146 (42%)	0.036	0	100 (41%)	0.273*
Breast cancer diagnosis prior to RRSO (%)	8 (50%)	355 (56%)	0.621	5 (42%)	209 (56%)	0.387	3 (75%)	146 (57%)	0.639
Mean age at breast cancer diagnosis (range)	42.6 (28.0–55.2)	42.2 (24.3–70.6)	0.886	37.9 (28.0–55.2)	40.2 (24.3–60.0)	0.475	50.4 (48.5–52.0)	44.9 (25.7–70.6)	0.233
Mean time from genetic testing to RRSO	0.86 (0.003–6.12)	1.01 (0–9.14)	0.679	0.94 (0.003–6.12)	1.03 (0–9.13)	0.835	1.10 (0.06–3.07)	1.39 (0.01–8.48)	0.833

*Exact confidence levels not possible with zero count cells

Table 2

Women diagnosed with occult Ovarian Cancer (OOC) versus non-Occult Ovarian cancer

Variable	Total sample			*BRCA1*			*BRCA2*		
	OOC (*N* = 16)	Ovarian cancer (*N* = 16)	*P*-value	OOC (*N* = 12)	Ovarian cancer (*N* = 12)	*P*-value	OOC (*N* = 4)	Ovarian cancer (*N* = 4)	*P*-value
Stage 1	6 (37.5%)	0	0.018*	6 (50%)	0	0.069*	0	0	
Stage 2	3 (18.75%)	5 (31.25%)		3 (25%)	4 (33.33%)		0	1 (25%)	
Stage 3	3 (18.75%)	5 (31.25%)		2 (16.67%)	4 (33.33%)		1 (25%)	1 (25%)	
Stage 4	1 (6.25%)	0		0	0		1 (25%)	0	
Stage Unknown	3 (18.75%)	6 (37.5%)		1 (8.33%)	4 (33.33%)		2 (50%)	2 (50%)	
Mean time to follow-up: testing to diagnosis, years (range)	0.86 (0.003–6.12)	1.45 (0.02–4.99)	0.326	0.94 (0.003–6.12)	1.45 (0.05–4.99)	0.481	0.61 (0.06–1.75)	1.45 (0.02–4.84)	0.509
Mean time to follow-up: diagnosis to last followup, years (range)	1.94 (0.07–6.05)	2.87 (0.07–6.50)	0.126	2.18 (0.07–6.05)	2.72 (0.07–6.50)	0.482	1.24 (0.48–1.65)	3.32 (2.36–4.50)	0.009
Alive at Follow-up	15 (94%)	14 (88%)	1.00	12 (90%)	10 (83%)	0.478*	3 (75%)	4 (100%)	1.00*
Died of ovarian cancer	1 (6.25%)	2 (12.35%)		0	2 (16.7%)		1 (25%)	0	

*Exact confidence levels not possible with zero count cells

Table 3

Recommendations for RRSO

Minimal Standards for RRSO	
1	All physicians caring for BRCA1 and BRCA2 mutation carriers should be made aware of their genetic status, including surgeons, radiologists and pathologists
2	At the time of RRSO, the pelvic cavity should be inspected for abnormalities
3	The ovaries and fallopian tubes should be removed as completely as possible
4	Ovaries and fallopian tubes should be examined in toto during pathologic review
The roles of the following in routine practice require additional study	
1	Peritoneal washings
2	Random omental biopsies
3	Hysterectomy