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Prospective Follow-up of Quality of Life for Participants Undergoing Risk-Reducing Salpingo-Oophorectomy or Ovarian Cancer Screening in GOG-0199: An NRG Oncology/GOG Study

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Abstract

Background—Risk-reducing salpingo-oophorectomy (RRSO) and ovarian cancer screening (OCS) are management options for women at increased risk of ovarian cancer. Long-term effects of these interventions on quality of life (QOL) are not well understood.

Methods—GOG-0199 is a prospective cohort study of women at increased ovarian cancer risk who chose either RRSO or OCS as their risk management intervention. At study entry, 6, 12, 24 and 60 months of follow-up, participants completed the QOL questionnaire, which included the Medical Outcome Study Short Form-36, the Impact of Events Scales, the Center for Epidemiological Studies Depression Scale, the State-Trait Anxiety Inventory, the Functional Assessment of Cancer Therapy – Endocrine Subscale, and the Sexual Activity Questionnaire. QOL measures were compared between the RRSO and OCS cohort at baseline and over time.

Results—Five-hundred-sixty-two participants in the RRSO cohort and 1,010 in the OCS completed the baseline and at least one follow-up questionnaire. At baseline, participants selecting RRSO reported lower health-related QOL (HRQOL), greater ovarian cancer-related stress, greater anxiety, and more depressive symptomatology, which improved during follow-up, especially for ovarian cancer-related stress. Screening was not found to adversely impact HRQOL. Hormone-related menopausal symptoms worsened and sexual functioning declined during follow-up in both cohorts, but more so among participants who underwent RRSO.

Conclusions—HRQOL improved after surgery among women who chose RRSO and remained stable among participants undergoing screening. The adverse effects of RRSO and screening on short-term and long-term sexual activity and sexual functioning warrant consideration in the decision-making process for high-risk women.

Introduction

Ovarian cancer (OC) risk is significantly increased in certain hereditary cancer syndromes, such as the Hereditary Breast/Ovarian Cancer syndrome (1, 2), and Lynch syndrome (3, 4).

Family history of OC, especially in first-degree relatives, has also been shown to be associated with increased risk (5). Risk management options for high-risk women are limited and uncertainties regarding these options remain. For *BRCA1* and *BRCA2* (*BRCA1/2)* mutation carriers, risk-reducing salpingo-oophorectomy (RRSO) has been shown to reduce ovarian/fallopian tube cancer incidence as well as cancer-specific and overall mortality, and is considered the most effective ovarian cancer risk management option (6–8). However, the efficacy of RRSO on risk reduction for women at increased risk based on personal and/or family cancer history, but who have no detectable germline pathogenic variant in known susceptibility genes, is not established. Moreover, RRSO is a major and irreversible intervention, often with significant short-term consequences, particularly symptoms related to estrogen deprivation and sexual dysfunction (9–14), and potential long-term morbidity and cardiovascular mortality risk, in pre-menopausal women due to the sequelae of premature menopause (15). Nonetheless, most studies of high-risk women undergoing RRSO have shown that short-term and long-term overall quality of health quality (QOL) was not adversely affected (9, 10, 16–18). For women who reported acute decreases in QOL after RRSO, these effects generally resolved within 12 months (19). Prospective long-term follow-up data on QOL after RRSO are limited. A recent small study showed that high-risk women who underwent RRSO reported more sexual discomfort and urogenital symptoms, but no differences in anxiety, depression, or body image, compared with age- and risk-matched controls, at 3 years' follow-up (20).

Although ovarian cancer screening (OCS) with periodic transvaginal ultrasound and serum CA125 measurements is often utilized as a risk management option, its effectiveness for high-risk women has not been demonstrated, and routine screening is not recommended (21–23). The need for testing over many years, and frequent false-positive screening results, may increase anxiety (24, 25). However, a study of average-risk women showed that serial CA-125 determinations did not incur any clinically significant psychological morbidity from repeat testing following abnormal screening results (26). For some high-risk women, participating in a screening program may decrease emotional distress due to reassurance from negative test results, or a sense of satisfaction from a proactive approach to risk management. However, the acceptability and long-term effects of OCS on QOL are unknown.

In this study, women considered to be at increased risk of OC based on family history of ovarian cancer or at least 20% probability of carrying a BRCA1 or BRCA2 pathogenic variant chose either RRSO or OCS at enrollment and were followed prospectively for five years. A primary study objective was to determine whether overall health-related QOL (HRQOL), depression, cancer-related stress, anxiety, menopausal symptoms, and sexual functioning differed at baseline and over time between women undergoing OCS and those who elected RRSO at baseline.

Methods

Study Population

GOG-0199 is a multi-institution, prospective cohort study. At enrollment, participants chose either RRSO (27) or OCS (28) utilizing the Risk of Ovarian Cancer Algorithm (ROCA), an

experimental screening methodology (29). Participants in the OCS cohort were screened according to ROCA (29), with CA-125 measurements and ROCA score calculations every 3 months and annual transvaginal ultrasound (TVUS). The ROCA score reflects the probability of harboring ovarian cancer (normal risk: <1%; intermediate risk: 1–10%; and elevated risk: >10%). Additional follow-up, including repeat CA-125 measurements, TVUS, and/or evaluation by a gynecologist oncologist or the study site Principal Investigator, was determined by the ROCA score. Participants who elected RRSO underwent the protocol-defined procedure within 90 days of enrollment. Hysterectomy was performed electively per patient and physician discretion. Participants in the RRSO cohort had CA-125 measurements and ROCA score calculations every 6 months during the study prospective follow-up period. Participants in the OCS cohort had the option to cross-over to the RRSO cohort post-enrollment, either electively or as prompted by screening results or clinical findings. Detailed eligibility criteria have been published previously (30). In brief, women aged ≥ 30, with no previous history of ovarian/fallopian tube/peritoneal cancer and had at least one intact ovary, were eligible if they or a close relative carried a *BRCA1/2* pathogenic variant, or if they had a personal and/or family history of BC and/or OC that conferred an increased OC risk, or ≥20% probability of carrying a *BRCA1/2* pathogenic variant based on the BRCAPRO model (31). The study opened to accrual 6/16/2003 and closed on 11/3/2006. Participants were followed prospectively for 5 years. By design, it was considered that 1,600 participants would provide a sufficiently representative sample for the QOL study endpoints. Thus, only participants enrolled prior to April 24, 2006 were asked to complete a QOL questionnaire at study entry, and at 6, 12, 24 and 60 months of follow-up.

All participants signed informed written informed consent for GOG Protocol 0199; NCI Protocol 02-C-0268; NCT-00043472 which were approved by institutional review boards at the National Cancer Institute, GOG and 151 GOG institutions (US, Australia).

Sociodemographic and Cancer History Information

We collected information on age, race, menopausal status, marital status, education, self reported *BRCA1/2* mutation status, personal history of BC, personal history of any cancer, and family history of BC, pre-menopausal BC, and OC. Self-reported mutation status at the time of enrollment was used in this analysis, since this measure best reflected participants' understanding of their mutation status.

Quality of Life Instruments

The QOL questionnaire included validated instruments to assess overall QOL, anxiety, depression, frequency of menopausal symptoms, and sexual functioning. The questionnaire was completed by participants at each indicated time-point, except for the time-point(s) that occurred after an off-study event, including cancer diagnosis (except non-melanoma skin cancers), pregnancy, withdrawal from participation, or death, or after loss to follow-up.

(1) The Medical Outcome Study Short Form-36 (MOS SF-36)—The MOS SF-36 is a validated 36-item patient-reported outcome measure designed to assess HRQOL across all medical conditions, consisting of eight subscales measuring general health perceptions, physical functioning, role limitations due to physical health problems, role limitations due to

emotional problems, bodily pain, vitality, social functioning, general mental health, and one item evaluating the change in health (32). Each subscale score was computed by summing subscale items and transforming the total to a 0–100 scale, where higher scores indicated better HRQOL.

(2) The Impact of Events Scale (IES)—The IES provides a quantitative measure of the impact of OC-related stress. It is a validated 15-item self-report instrument focusing on intrusive thoughts and avoidance associated with a stressor, in this case OC risk and its associated management options (33, 34). The overall score (range 0–75) was calculated based on the individual responses. Higher scores indicated more stress. The overall score was also used to classify participants' level of stress as subclinical (<9 points), mild (9–25 points), moderate (26–43 points), or severe (≥44 points), delineating levels of clinical significance.

(3) The Center for Epidemiology Studies Depression Scale (CES-D)—The CES-D is a 20-item instrument used to assess depressive symptoms, including depressive mood and feelings of helplessness, over the previous 7 days. Responses were summed to provide an overall score (range 0–60). A score of 16 or higher is indicative of significant depressive symptomatology (35).

(4) Speilberger State-Trait Anxiety Inventory (STAI)—The STAI consists of two 20-item subscales which measure state and trait anxiety (36). State anxiety is a transitory emotional response to a stressful situation and reflected how the individual felt at the time the instrument was administered. Trait anxiety reflected a stable predisposition to anxiety as determined by personality pattern. Scores for each sub-scale ranged from 20 to 80, with higher scores indicating greater anxiety.

(5) The Functional Assessment of Cancer Therapy – Endocrine Subscale (FACT-ES)—The FACT-ES is a validated 18-item scale designed to measure hormone-related symptoms (37) over the 7 days prior to completing the instrument. An overall total score was calculated by summing the individual score for each item (range 0–72). Higher scores represented fewer hormone-related symptoms.

(6) The Sexual Assessment Questionnaire (SAQ)—The SAQ is a 14-item questionnaire designed to capture information regarding variation in sexual functioning in three parameters: pleasure from intercourse, pain from intercourse, and change of sexual habit (38). The sexual pleasure (range 0–18) and discomfort (range 0–6) subscale scores were calculated by summing the item scores after the negative items were reversed. Higher scores indicated better sexual functioning.

Statistical Analysis

Participants were included if they completed the baseline questionnaire and ≥1 follow-up questionnaire(s). Participants in the OCS cohort who had RRSO during follow-up were censored at the time of RRSO, and their post-RRSO QOL assessments were excluded from the analysis.

Sociodemographic characteristics, health-related factors, and personal and family cancer history were compared between the RRSO and OCS cohorts, using chi-square and t-tests for categorical and continuous variables, respectively.

Questionnaire completion rate was calculated at each time-point using the number of participants expected to complete the assessment for that time-point as the denominator, and was compared between the two cohorts using the generalizing estimating equations for repeated measures. A logit link for the binomial distribution was used to model the completeness status (yes/no) and an unstructured working correlation matrix was used to model the correlation of the repeated measures from the same subject.

For baseline QOL measures, a general linear model was used to examine the differences between the two cohorts with adjustment for age, previous BC (yes/no), mutation status at baseline (carrier/non-carrier/unknown), and contraceptive use (current/previous use/never). For measures reported over time, a linear mixed model was used to assess the group differences over time, adjusting for baseline scores and age. The time-points were treated as categorical, and the covariance matrix for repeated measures was assumed to be unstructured. To reflect the observed covariance pattern of the QOL scores, the 'empirical' variance was used in estimating the precision of parameter estimates. The interaction between time-points and study cohort was tested first for the constant group difference over time. If the interaction effect was not statistically significant, an overall group difference was evaluated by an average of estimates from each time-point together with a 99% confidence interval. To adjusting for multiple testing and limit the overall type I error, the Sidak method $1-(1-\text{unadjust\_p})^{18}$ was used to adjust the group difference p-values for each measure.

All analyses were performed using the SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Results

One-thousand-seven-hundred-eighty participants enrolled prior to April 24, 2006. One-hundred-eleven participants in the OCS and 97 participants in the RRSO cohort were excluded (Figure 1). Questionnaire completion rates declined over time, with more participants in the OCS cohort completing the questionnaires at each time-point compared with the RRSO cohort ($p<0.001$, Table 1).

Participants in the RRSO cohort were older than those in the OCS cohort (48.6 years *vs.* 47.6 years, $p=0.038$) and were more likely to report being a *BRCA1* or *BRCA2* mutation carrier, have a personal history of BC, and to not be using contraceptive at the time of enrollment (Table 2).

(1) The Medical Outcome Study Short Form-36 (MOS SF-36)

At baseline, participants in the RRSO cohort had significantly lower Physical Functioning, Social Functioning, Role Functioning_Physical, and Role Functioning_Emotional subscale scores than OCS participants. The baseline scores did not differ significantly between the

two cohorts for the Bodily Pain, Mental Health, Vitality, and General Health subscales (Table 3).

Over time, the group difference did not vary significantly for any subscales, and there were no significant group differences in HRQOL as assessed by any MOS SF-36 subscale (Supplemental Figure S1 and Table 4). However, the group differences were significantly larger in participants age 50 years and younger for the bodily pain (−4.5 (−7.4 to −1.6) vs. 0.2 (−3.3 to 3.5), $p_{interaction}$=0.007) and vitality (−4.0 (−6.4 to −1.6) vs. 0.8 (−2.1 to 3.6), $p_{interaction}$=0.001) subscales, with those in the OCS group reported better QOL than those in the RRSO group in these aspects.

(2) The Impact of Events Scale (IES)

At baseline, participants in the RRSO cohort reported higher IES Global score and Intrusion and Avoidance subscale scores than those in the OCS cohort (Table 3). The IES global scores declined significantly during follow-up (p<0.001), most notably within 6 months after RRSO (Supplemental Figure S2A). After adjusting for the baseline score, the patients in the RRSO cohort reported a statistically significantly lower global and component scores compared with the OCS cohort (Table 4). There were no significant changes in the group differences over time ($p_{interaction}$=0.6). The reduction in the overall global score was largest among participants who had tested positive for a BRCA mutation prior to enrollment (positive: (−6.3 (−8.5 to −4.1) vs. negative: −5.0 (−7.6 to −2.4) vs. unknown: −3.5 (−5.0 to −2.0); $p_{interaction}$=0.02).

At baseline, more participants in the RRSO cohort reported clinically significant levels (*i.e.,* IES global score ≥ 9) of OC-related stress (60% vs 41%, p<0.001). In general, during follow-up, participants in the RRSO group were less likely to report clinical levels of OC-related stress (odds ratio=0.42; 99%CI=0.31 to 0.57; $p_{adjusted}$<0.001). Over time, the percentages of patients with clinical levels of stress declined in both groups (p_{time}<0.001), but the difference between the two groups remained unchanged ($p_{interaction}$=0.2, Supplemental Figure S2B).

(3) The Center for Epidemiology Studies Depression Scale (CES-D)

At baseline, the RRSO cohort scored 1.4 points higher on the CES-D than the OCS cohort (p=0.006, Table 3), and more participants scored ≥16, the threshold suggestive of clinical depression (21% vs 15%, p=0.007). The group difference in the CES-D scores did not change significantly during follow-up ($p_{interaction}$=0.02, Supplemental Figure S3A), with an estimated overall difference between the two cohorts of 0.8 (Table 4). No overall difference between the two cohort by mutation status was observed (data not shown). There was no difference in the percentages of participants with clinical depression between the two groups ($p_{adjusted}$=1.0, Supplemental Figure S3B).

(4) Speilberger State-Trait Anxiety Inventory (STAI)

At baseline, participants in the RRSO cohort reported higher STAI-State scores than, and similar STAI-Trait score to, those in the OCS cohort (Table 3). The two subscale scores did not change significantly over time (STAI-State, $p_{interaction}$=0.7; STAI-Trait, $p_{interaction}$=0.2,

Supplemental Figure S4), and there were no significant overall group differences in either subscale between the RRSO and OCS cohorts during follow-up (Table 4). There was no difference in either subscales between the two cohort by mutation status (data not shown).

(5) The Functional Assessment of Cancer Therapy – Endocrine Subscale (FACT-ES)

At baseline, participants in both groups reported similar levels of menopausal symptoms (Table 3). Over time, however, the FACT-ES scores declined significantly in the RRSO cohort, reflecting worsening menopausal symptomatology ($p<0.001$, Supplemental Figure S5), with significant changes between group differences across the time-points ($p_{interaction}=0.008$), and an estimated overall group difference of −2.6 (Table 4). The greatest difference between the two groups occurred at 24 months (RRSO vs OCS: −3.07, 99%CI= −4.1 to −2.04; $p_{adjusted}$ <0.001). By 60 months, the difference had decreased to −1.55 (99%CI=−2.72 to −0.38; $p_{adjusted}<0.011$).

(6) The Sexual Assessment Questionnaire (SAQ)

Sexual functioning, as measured by reported pleasure from intercourse, pain from intercourse, and change of sexual habit, was evaluated among patients who reported engaging in sexual activities at the assessment time points. Approximately 70% of participants (391 in the RRSO and 711 in the OCS cohort) reported on measures related to sexual health at baseline, vs 65%, 62%, 53% and 37% at 6, 12, 24, and 60 months, respectively.

SAQ_Pleasure—The SAQ_Pleasure subscale scores were not statistically different between the two groups at baseline (Table 3); however, the scores declined significantly in both cohorts during follow-up ($p_{time}<0.001$, Supplemental Figure S6A), with significant differences between the two cohorts at each of the time-points (RRSO scoring worse), and an overall group difference of −0.93 (Table 4). These group differences did not vary significantly over time ($p_{interaction}=0.2$).

SAQ_Discomfort—The SAQ_Discomfort scores were not different between the RRSO and OCS cohorts at baseline (Table 3). The SAQ_Discomfort subscale scores declined significantly during follow-up ($p_{time}<0.001$, Supplemental Figure S6B), with an estimated overall group difference between the two cohorts of −1.06 (RRSO scoring worse) (Table 4). The group difference did not vary significantly over time ($p_{interaction}=0.2$).

SAQ_Habit—At baseline, SAQ_Habit subscale scores were 0.08 units lower for the RRSO group compared with the OCS group (Table 3). Over time, participants in the RRSO cohort continued to have lower scores than participants in the OCS cohort, with an estimated overall group difference of −0.11 (Table 4). The group differences ($p_{interaction}=0.2$) did not change significantly over time (Supplemental Figure S6C).

Discussion

In this study of women who selected either RRSO or OCS as the option for managing increased OC risk, we collected information on QOL using various metrics at baseline and

prospectively for 5 years. Approximately 48% of participants in the RRSO cohort reported themselves to have a *BRCA* pathogenic variant, compared with 16% in the OCS cohort, which might explain in part the lower baseline QOL measures in the RRSO cohort. At baseline, participants selecting RRSO reported lower HRQOL as indicated by the SF-36, greater OC-related stress, greater anxiety, and more depressive symptomatology – suggesting that OC-related worry might have had a stronger impact on their overall well-being compared with participants who chose OCS. At 6 months after enrollment, these scores had improved to levels either similar to or exceeding those reported by participants in the OCS cohort. The improvement was strongest for OC-related stress, especially among those who were known to have a *BRCA* pathogenic variant at enrollment. Throughout the study, among those age 50 years and younger, participants the RRSO reported higher bodily pain and lower vitality than participants in the OCS, suggesting that RRSO had a greater impact on these aspects of the HRQOL among younger individuals. Although the financial burden of RRSO was not formally assessed in this study, its impact might not have substantially affected QOL, as evidenced by the improvement in the RRSO cohort's QOL at the 6-month timepoint. Similarly, frequent blood draw and ROCA measurements could potentially result in substantial financial burden; however, this did not appear to have adversely affected the QOL in this study. Furthermore, serial CA-125 determinations among average-risk women has been shown to not associated with clinically significant psychological morbidity from repeat testing (26). Thus, although the impact of interval ROCA measurement after RRSO cannot be quantified, it was unlikely to be significant, as there was still an overall improvement in QOL in this cohort. Subsequent measures over time showed that QOL as measured by the SF-36, IES, STAI, and CES-D were either similar in both groups or better in the RRSO cohort, possibly due to their post-surgical reduction in cancer worry.

More participants in the OCS cohort than in the RRSO cohort had not undergone genetic testing prior to enrollment. Not knowing their *BRCA* mutation status might have an impact on the participants' perception of cancer risk and cancer worries. However, QOL measures at baseline were adjusted by *BRCA* mutation carrier status, and the linear mixed model used to assess differences in the repeated measures over time was adjusted for baseline scores. Thus, it is unlikely that not knowing their mutation status influenced the findings regarding QOL measures over the study duration.

Previous studies among individuals with a *BRCA* pathogenic variants unaffected with cancer showed that general QOL was not permanently affected by their management choices (39). Although frequent screening and the consequent need for additional testing to evaluate false-positive findings have been associated with elevated anxiety levels among high-risk women (24, 25), we hypothesized that participating in an active, long-term screening program might decrease emotional distress by helping women feel proactive in their care and reassured by normal screening tests. Our data suggest that long-term, frequent screening did not adversely impact the HRQOL among participants undergoing OCS.

Hormone-related menopausal symptoms and self-reported sexual functioning were similar between the two study groups at baseline. However, compared with women in the OCS cohort, participants in the RRSO cohort reported worsened menopausal symptoms, reduced

sexual pleasure, more intercourse-related discomfort, and less frequent sexual activity during follow-up, which reached a nadir at 6-months, and then stabilized after 24 months. Similar findings on the effect of RRSO on sexual activity and sexual functioning have been reported previously (12, 20, 40). While hormone replacement therapy (HRT) appears to ameliorate post-RRSO sexual discomfort compared with nonusers (40) high-risk women may have concerns about cancer risks associated with HRT. However, more recently data showed that HRT after RRSO was safe in women with a *BRCA1* pathogenic variant without a personal history of breast cancer (41). In this study, 18% of participants in the RRSO cohort reported HRT use prior to and after surgery. No participants who were not already on HRT started taking it after RRSO. Unfortunately, we did not collect data on why HRT was not utilized, and approximately 56% of the participants in the RRSO cohort had a prior history of breast cancer, which would have precluded HRT use. It is likely that for women with a *BRCA1* pathogenic variant with no previous history of breast cancer, the use of HRT would have lowered the worsening in menopausal symptoms and sexual functioning.

Our study has some limitations. Questionnaire response rates declined significantly over time, as is typical in long-term studies, with ~60% of the eligible participants completing the questionnaire at 60 months. Our results could have been biased if participants with worse QOL disproportionately did not complete the questionnaire. Efforts were made to reduce the burden related to data collection. The form was mailed to participants, who could return it by mail or in person at their annual visit. These measures might have facilitated our achieving a reasonable 5-year response rate in this large cohort. Second, ~96% of the participants were white, which might limit our ability to apply these findings to other racial/ethnic groups, and it is not clear how changes in QOL might differ between whites and non-whites.

The study's large sample size, broad recruitment base (including many community oncology programs), and the inclusion of individuals at increased OC risk, either due to a *BRCA1/2* pathogenic variant or a positive family-history, increase the representativeness and applicability of our findings. The QOL data were collected prospectively, using validated psychometric instruments, over a 5-year period. Thus, the findings reflect the long-term effect of RRSO and OCS on women at increased OC risk, an area in which currently available data are limited.

Our data showed that cancer worry and depression symptomatology decreased, and general HRQOL improved, soon after surgery among women undergoing RRSO, and remained stable during the 5-year follow-up. Screening, on the other hand, did not significantly impact long-term QOL. It is reassuring to demonstrate that concerns regarding the psychological and emotional burdens of an intensive OCS program might not be justified. Although there is no effective ovarian cancer screening regimen available, this knowledge might be useful in future efforts to establish such a regimen. Women who elected RRSO reported worsening menopausal symptoms and poorer sexual activity and sexual functioning scores. Issues regarding the effect of surgery on short-term and long-term sexual activity and sexual functioning should be discussed thoroughly in the decision-making process. However, current understanding of medical management post-RRSO, including the judicious use of

hormone therapy, should be part of the discussion. These data can inform the discussions with women at increased OC risk regarding their decision about RRSO.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CONFLICTS OF INTEREST

Dr. Kelly Wilkinson received payment for lectures, including service on speakers bureaus from Tessaro-Speakers Bureau.

Dr. Robert Wenham received an institutional grant for conducting research from the GOG. He also served as a consultant for Tesaro as a DSMB Chair and Genentech on the Advisory Board. He received grants/grants pending from Merck for investigator initiation of study. He also received payment for lectures, including service on speakers bureaus from Genentech, Tesaro, Clovis and J&J.

Dr. Matthew Powell served as a consultant for Roche/Genentech, Merck, Clovis Oncology, Tesaro, and AstraZeneca. He also received payment for lectures, including service on speakers bureaus from Roche/Genentech, AstraZeneca, Clovis Oncology, Tesaro and Merck.

Dr. Lari Wenzel was a consultant for Janssen, Lilly and EMD Serona.

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RESEARCH HIGHLIGHTS

- Ovarian cancer screening did not adversely impact health-related Quality of Life
- Health-related QOL improved during follow-up for participants selecting RRSO
- Ovarian cancer-related stress improved after RRSO
- No adverse effects of RRSO or OCS on psychological and emotional well-being

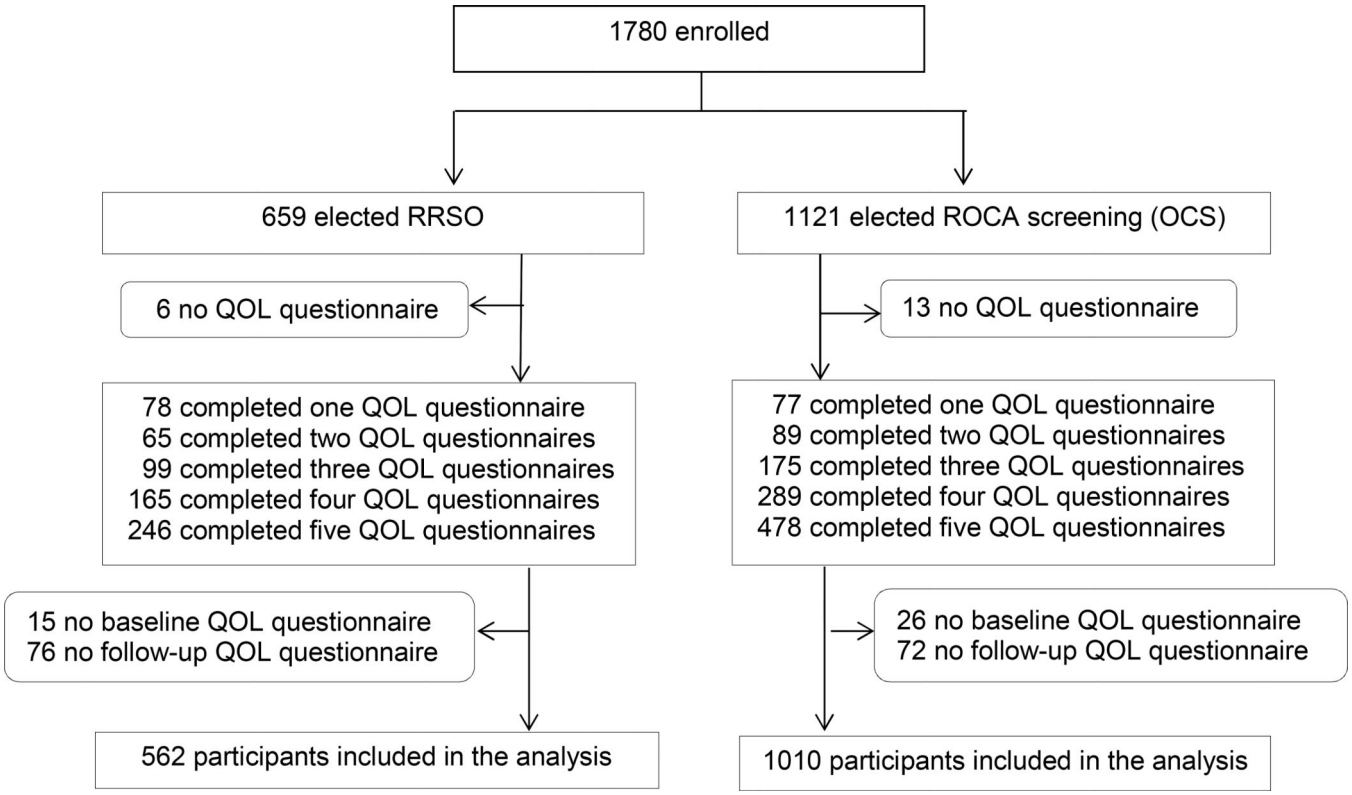

Figure 1:
CONSORT diagram

Table 1:

Questionnaire completion at each time-point by cohort

Assessment time	Status of PROs assessment	RRSO	Screening
Baseline	Expected	659	1121
	Received and Valid	638(97%)	1082(97%)
	Received but with Insufficient answer	6	12
	Missed without reasons	15	27
6 Months	Death (cumulative)	0	1
	Cancer diagnosis	18	7
	Withdrew consent	3	8
	Pregnancy	0	2
	Expected	638	1103
	Received and Valid	528(83%)	952(86%)
	Received but with Insufficient answer	4	13
	Patient refusal	8	6
	Missed without reasons	98	132
12 Months	Death (cumulative)	0	1
	Cancer diagnosis (cumulative)	23	19
	Withdrew consent (cumulative)	20	30
	Pregnancy (cumulative)	0	6
	Expected	616	1065
	Received and Valid	492 (80%)	907 (85%)
	Received but with Insufficient answer	8	7
	Patient refusal	15	19
	Missed without reasons	101	132
24 months	Death (cumulative)	2	2
	Cancer diagnosis (cumulative)	33	41
	Withdrew consent (cumulative)	39	65
	Pregnancy (cumulative)	0	15
	Expected	585	998
	Received and Valid	424(72%)	799(80%)
	Received but with Insufficient answer	1	5
	Patient refusal	31	49
	Missed Without reasons	129	145
60 months	Death (cumulative)	8	16
	Cancer diagnosis (cumulative)	51	63
	Withdrew consent (cumulative)	67	145
	Pregnancy (cumulative)	0	33
	Expected	533	864
	Received and Valid	313(59%)	586(68%)

Assessment time	Status of PROs assessment	RRSO	Screening
	Received but with Insufficient answer	1	7
	Patient refusal	102	130
	Missed Without reasons	117	141

RRSO: risk-reducing salpingo-oophorectomy; OCS: ovarian cancer screening

Table 2:

Baseline characteristics

	RRSO (n=562)		OCS (n=1010)		
Patient characteristic	**N**	**%**	**N**	**%**	**P-value**
Age group					
30–39	96	17.08	274	27.13	
40–49	239	42.53	321	31.78	
50–59	170	30.25	301	29.80	<0.001
60–69	47	8.36	100	9.90	
≥70	10	1.78	14	1.39	
Race					
White	540	96.1	977	96.7	
Black	16	2.9	20	2.0	0.51
Other/Not Specified	6	1.1	13	1.3	
Menopausal status					
Pre-menopausal	315	56.1	610	60.4	0.09
Menopausal	247	44.0	400	39.6	
Ashkenazi Parent					
Yes	108	19.2	222	22.0	
No	410	73.0	732	72.5	0.12
Unknown/Not specified	44	7.8	56	5.5	
Self-reported mutation status					
Known carrier	267	47.5	160	15.8	
Known non-carrier	49	8.7	196	19.4	
Tested but results unknown	47	8.4	57	5.6	<0.001
Not tested	193	34.3	583	57.7	
Unknown	6	1.1	14	1.4	
Previous breast cancer					
Yes	313	55.7	419	41.5	<0.001
No	249	44.3	591	58.5	
Parity					
Nulliparous	155	27.6	307	30.4	0.66
Parous	407	72.4	702	69.6	
Hormone therapy currently					
Yes	100	17.8	188	18.6	
No	462	82.2	819	81.1	0.40
Unknown			3	0.3	
Contraceptive use					

	RRSO (n=562)		OCS (n=1010)		
Patient characteristic	**N**	**%**	**N**	**%**	**P-value**
Yes, currently	38	6.8	127	12.6	
Yes, not currently	390	69.4	637	63.1	0.001
Never used	134	23.8	246	24.4	

RRSO: risk-reducing salpingo-oophorectomy; OCS: ovarian cancer screening

Table 3:

Least Square Means differences at baseline

QOL Instruments	RRSO	OCS	RRSO-OCS	p-value*
	Mean (SD)	Mean (SD)	LS-Means* Difference (95% CI)	
The Medical Outcome Study Short Form-36				
Physical functioning	86.4 (19.7)	90.6 (15.5)	−3.6 (−5.5 to −1.7)	<0.001
Role functioning_physical	77.8 (36.9)	86.4 (28.5)	−7.4 (−10.9 to −3.9)	<0.001
Role functioning_emotional	80.3 (35.6)	86.5 (28.6)	−5.1 (−8.6 to −1.6)	0.004
Social functioning	82.0 (23.7)	88.0 (19.3)	−5.6 (−7.9 to −3.2)	<0.001
Bodily pain	76.1 (25.6)	77.6 (22.5)	−1.4 (−4.0 to 1.2)	0.30
Mental health	74.3 (17.1)	75.4 (15.5)	−0.87 (−2.7 to 0.9)	0.34
Vitality	59.7 (21.7)	61.2 (20.5)	−1.7 (−4.0 to 0.6)	0.14
General health	73.9 (19.4)	75.4 (18.5)	−0.97 (−3.1 to 1.1)	0.36
The Impact of Events Scales				
Overall score	16.4 (15.3)	10.4 (13.2)	5.5 (4.0 to 7.0)	<0.001
Intrusion	7.4 (8.0)	4.2 (6.0)	3.1 (2.4 to 3.9)	<0.001
Avoidance	9.0 (8.6)	6.2 (8.1)	2.4 (1.4 to 3.3)	<0.001
Center for Epidemiological Studies Depression Scale				
CES-D	9.6 (9.9)	8.1 (8.5)	1.4 (0.4 to 2.4)	0.006
State-Trait Anxiety Inventory				
State of Anxiety	46.0 (12.0)	44.2 (11.0)	1.9 (0.6 to 3.1)	0.004
Trait of Anxiety	41.9 (10.7)	41.2 (10.0)	0.6 (−0.3 to 2.0)	0.15
The Functional Assessment of Cancer Therapy – Endocrine Subscale				
FACT-ES	60.1 (8.3)	60.7 (8.2)	−0.9 (−1.8 to 0.05)	0.06
Sexual Activity Questionnaire				
Pleasure	11.6 (4.7)	12.2 (4.4)	−0.4 (1.0 to 0.2)	0.2
Discomfort	4.1 (2.0)	4.3 (1.9)	−0.2 (−0.4 to 0.1)	0.16
Habit	0.7 (0.6)	0.9 (0.6)	−0.04 (−0.16 to −0.002)	0.05

RRSO: risk-reducing salpingo-oophorectomy; OCS: ovarian cancer screening

*Least-Square Means difference and p-values were from a fitted linear model with adjustment for patient's age, status of previous breast cancer (yes/no), mutation status (carrier/non-carrier/unknown), and contraceptive use (current/previous/never) at baseline.

Table 4:

Overall group differences between RRSO and OCS

QOL Instruments	LS-Means group difference (99% CI)	Adjusted p-value*	Unadjusted p-values for interaction
The Medical Outcome Study Short Form-36			
Physical functioning	0.09 (−1.3 to 1.48)	1.0	0.4
Role functioning_physical	−0.09 (−3.06 to 2.89)	1.0	0.6
Role functioning_emotional	−0.41 (−3.34 to 2.51)	1.0	0.4
Social functioning	−0.15 (−2.33 to 2.03)	1.0	0.05
Bodily pain	−2.11 (−4.37 to 0.15)	0.3	0.5
Mental health	−0.37 (−1.92 to 1.18)	1.0	0.3
Vitality	−1.61 (−3.53 to 0.31)	0.4	0.06
General health	−1.28 (−2.86 to 0.31)	0.5	0.1
The Impact of Events Scales			
Overall score	−4.27 (−5.32 to −3.21)	<0.001	0.6
Intrusion	−1.75 (−2.21 to −1.29)	<0.001	0.8
Avoidance	−2.2 (−2.9 to −1.53)	<0.001	0.3
Center for Epidemiological Studies Depression Scale			
CES-D	0.08 (−0.79 ~ 0.95)	1.0	0.02
State-Trait Anxiety Inventory			
State of Anxiety	−0.7 (−1.74 to 0.34)	0.8	0.7
Trait of Anxiety	0.32 (−0.56 to 1.2)	1.0	0.2
The Functional Assessment of Cancer Therapy – Endocrine Subscale			
FACT-ES	−2.6 (−3.37 to −1.83)	<0.001	0.008
Sexual Activity Questionnaire			
Pleasure	−0.93 (−1.48 to −0.37)	<0.001	0.2
Discomfort	−1.06 (−1.34 to −0.78)	<0.001	0.2
Habit	−0.11 (−0.18 to −0.04)	<0.001	0.2

RRSO: risk-reducing salpingo-oophorectomy; OCS: ovarian cancer screening

* p-values for testing least squares means differences estimated from the fitted mixed model adjusting for baseline score, age at enrollment, assessment time, and interaction between time and groups, and adjusted for multiple testing using Sidak method.