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RISK FACTORS FOR SEXUAL DYSFUNCTION IN BRCA MUTATION CARRIERS FOLLOWING RISK-REDUCING SALPINGO-OOPHORECTOMY

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Abstract

Objective—To identify risk factors for sexual dysfunction, in BRCA mutation carriers who have undergone risk-reducing salpingo-oophorectomy (RRSO)

Methods—A cross-sectional study was performed. *BRCA1/2* mutation carriers with and without RRSO were surveyed to determine sexual function (Female Sex Function Index [FSFI]), demographics, medical history, sleep quality, depression and anxiety scores. Characteristics of patients with the lowest quartile of FSFI scores ($<14 \pm 8.8$) were analyzed to identify risk factors for the most severe phenotype.

Results—In the 804 women surveyed, 764 underwent RRSO. Of the 529 (69%) carriers with completed FSFI questionnaires in the RRSO cohort, sexual dysfunction was reported in 77.3%. Poor sleep ($p=0.002$), hot flashes ($p=0.002$), lack of current systemic hormone therapy (HT) use ($p=0.002$), depression ($p<0.001$), and anxiety ($p=0.001$) were associated with sexual dysfunction. In adjusted analyses, depression (aOR 2.4, 95% CI 1.4–4.1) and hot flashes (aOR 1.9, 95% CI 1.2–3.0) remained significantly associated with sexual dysfunction. Depression was also a significant risk factor for the most severe degree of sexual dysfunction (OR 2.1, 95% CI 1.3–3.5) and had the greatest impact on Arousal and Satisfaction domain scores of the FSFI. Current systemic HT use appeared to decrease the risk for sexual dysfunction (aOR 0.6, 95% CI 0.4–1.0).

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None

Conclusions—Sexual dysfunction is highly prevalent in BRCA mutation carriers following RRSO. Depression appears to be a significant risk factor for sexual dysfunction in this patient population and may be under-recognized and undertreated. Patient and provider education on sexual side effects following surgery and risk factors for sexual dysfunction is necessary to decrease post-operative sexual distress. HT may be associated with improved sexual function following surgery.

Keywords

surgical menopause; brca; mutation; risk-reducing salpingo-oophorectomy; sexual dysfunction

INTRODUCTION

Women who carry BRCA mutations have an increased lifetime risk of breast and ovarian cancer^{1,2}. Risk-reducing salpingo-oophorectomy (RRSO) is recommended to *BRCA1/2* mutation carriers by age 40 or after completion of childbearing³ and has been associated with significant reduction in ovarian, fallopian tube, peritoneal and breast cancer incidence, and improved survival^{4–6}.

While survival benefit and cancer reduction from RRSO are clearly advantageous, the consequences of early surgical menopause are less well understood, especially regarding quality of life (QOL) concerns including sexual function. Decreased pleasure, frequency, and comfort during sexual activity have been noted in women who have undergone RRSO^{7–10}. Vaginal dryness, changes in sexual interest, and changes in sex life are amongst the most common menopausal symptoms following surgery; regrettably, many women report feeling that they received inadequate sexual counseling preoperatively¹¹.

As genetic testing for hereditary cancers gains wider utilization, and as more women are found to have BRCA mutations and recommended to undergo RRSO, the need for improved counseling about the impact of RRSO on sexual function is imperative in this unique population. Thus, our objective was to determine the prevalence of sexual dysfunction in *BRCA1/2* carriers following RRSO and identify factors associated with sexual dysfunction after surgery. We hypothesized that concurrent depression and anxiety worsened sexual functioning after RRSO and that hormone therapy was associated with better sexual functioning.

MATERIALS AND METHODS

Study participants

Known *BRCA1* and/or *BRCA2* mutation carriers were recruited from the Bassett hereditary cancer risk clinics at the University of Pennsylvania through an in-person encounter or invitational letter. Participants were also recruited through a partnership with the Facing Our Risk of Cancer Empowered (FORCE) hereditary breast and ovarian cancer advocacy group. FORCE has an existing database of approximately 20,000 individuals interested in hereditary risk factors of breast and ovarian cancer who voluntarily receive information on a regular basis. Information about this study was posted in the FORCE monthly newsletter and

on the FORCE website. Women interested in participation were directed to the Basser Center website, which contained full study details and contact information for study coordinators. Women who were 30 years old and over, who had or were planning to undergo RRSO during the enrollment period (March 2013-March 2014) were eligible for participation. The primary aim of this study was to examine risk factors for sexual dysfunction following RRSO. We included as a comparison group *BRCA1/2* individuals who had not yet undergone surgery to isolate the effect of RRSO. Study participants provided informed consent and completed an online questionnaire comprised of sociodemographic information (age, race, ethnicity, marital/domestic partnership status, education and income level), medical diagnoses, medication usage, cancer history, and social history. Menstrual history, hormone therapy usage, fertility, and reproductive histories were also obtained. Validated survey instruments for quality of life indicators and sexual functioning were administered as part of the questionnaire. The University of Pennsylvania Institutional Review Board approved this study.

Instruments

The Female Sexual Function Index (FSFI) questionnaire was used to collect measures of sexual function overall and in six specific domains (Desire, Arousal, Lubrication, Orgasm, Satisfaction and Pain)¹². Test-retest reliability coefficients for each of the domains range from $r = 0.79$ to 0.86 with a high degree of internal consistency (Cronbach's alpha values of > 0.82). A total FSFI score of ≤ 26.55 is indicative of sexual dysfunction¹³.

The Hospital Anxiety and Depression Scale (HADS) was used to assess clinically significant generalized anxiety and depression¹⁴. This validated questionnaire is divided into two subscales: one for anxiety (HADS-A) and depression (HADS-D), respectively. Score for each subscale (anxiety and depression) can range from 0-21 as follows: normal (0-7), borderline (8-10) and abnormal or "case" (11-21).

The Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep quality over a one-month period¹⁵. A global score greater than 5 is indicative of poor sleep.

Statistical Analysis

Chi-square, student's *t*-test, Mann-Whitney U, and Fisher's exact tests were used as indicated to make between group comparisons of demographic characteristics, medical history, cancer history, surgical history, medication history and quality of life measures (vasomotor symptoms, PSQI, HADS-A and HADS-D). Initial comparisons were made between women who had completed an RRSO with those who had not yet undergone RRSO to isolate the role of oophorectomy in the *BRCA1/2* positive population. Subsequent analyses focused on post-RRSO cohort to compare potential risk factors for sexual dysfunction between those who had sexual dysfunction (FSFI ≤ 26.55) versus those who did not (FSFI > 26.55). To identify those participants with the most severe sexual dysfunction, we took the full distribution of women with an FSFI ≤ 26.55 and classified this group into quartiles. We performed a subanalysis of those who had the most severe sexual dysfunction as reflected by FSFI scores in the lowest quartile (FSFI summary score < 14) and compared them to the women with sexual dysfunction in the upper quartiles. Multivariable logistic

regression was used to identify risk factors for sexual dysfunction, including partner status, smoking, obesity, depression, anxiety, poor sleep, sex in the last year, cancer history, prior chemotherapy, prior mastectomy, history of hysterectomy, hot flashes, age at final salpingo-oophorectomy, HT and psychiatric medication use. Ultimately, logistic models for sexual dysfunction were adjusted for age and obesity. Each covariate was fit one at a time, and variables were entered into the model if the p value was <0.1 in unadjusted analysis. Each FSFI domain (Desire, Arousal, Lubrication, Orgasm, Satisfaction and Pain) was examined separately to determine risk factors for the lowest domain-specific quartile scores. A subgroup analysis of women under the age of 50 with no history of cancer was performed to isolate the effect of somatic age on sexual function. A significance level of 0.0167 was used to account for multiple comparisons. Data were analyzed using STATA version 13 (College Station, TX).

RESULTS

Cohort characteristics

Of the 804 women surveyed, 87% (n=700) of participants were recruited from FORCE and the remainder from outpatient clinics. The majority (n=764) had undergone RRSO, while 40 had not yet undergone surgery at the time of survey (Figure 1). Table 1 describes the baseline characteristics of the cohort. Patients who had undergone RRSO (and completed the FSFI) were older at the time of survey completion (47.6 vs. 35.7 years, $p<0.001$), more likely to have a history of cancer, chemotherapy, prior hysterectomy, or have undergone prior mastectomy compared to those who had not undergone RRSO ($p < 0.001$ for all). RRSO was associated with a lower mean FSFI summary score overall (19.2 vs. 27.9, $p<0.001$). If we consider age at the time of survey for the entire population, we found that age was significantly associated with an elevated odds of sexual dysfunction (OR 1.04, 95% CI 1.02-1.07, $p=0.001$). However, once we controlled for whether or not they had undergone RRSO, the association was no longer significant (adjusted OR 1.03, 95% CI 0.997-1.05, $p=0.08$). There was a higher percentage of patients with either case or borderline depression in the RRSO group (36.4% vs. 11.4%, $p=0.003$) and the majority experienced hot flashes (65.6% vs. 27.5%, $p<0.001$).

Of those who did not complete the FSFI, 61 women did not answer any FSFI questions, an additional 100 women reported no sexual activity, and the remainder had skipped questions within the FSFI and thus did not have a FSFI summary score for analysis. The FSFI cannot be completed unless the participant is partnered, as there is at least one item that refers to a partner. Those who completed the FSFI were younger at the time of the survey (46.5 vs. 50.2 years, $p < 0.001$) and at the time of RRSO (43.4 vs. 46.9 years, $p<0.001$), more likely to be married/in a domestic partnership (83.9 vs. 63%, $p<0.001$), to have had sex in the last year (89.2 vs. 28.1%, $p < 0.001$), had a prior hysterectomy (55.6 vs. 44.3%, $p=0.047$) and less likely to have poor sleep (58.2 vs. 72.3%, $p=0.02$).

Prevalence of and Risk Factors for Sexual Dysfunction

For the total cohort surveyed, patients who retained their ovaries were 60% less likely to experience sexual dysfunction as compared with those who had undergone RRSO (aOR 0.4,

95% CI 0.2-0.9, $p=0.02$). Of those who underwent an RRSO, 409 (77.3%) women reported sexual dysfunction. When comparing those with and without sexual dysfunction, both groups were comparable with respect to premenopausal status at the time of RRSO (48.4 vs. 49.2% $p = 0.67$), age (46.8 vs. 45.5 years, $p=0.10$), age at the time of RRSO (43.6 vs. 42.5 years, $p=0.15$), current partner status (married or in domestic partnership – 90.7 vs. 85.8%, $p=0.11$), history of prior hysterectomy (53.5 vs. 62.5%, $p=0.09$) and time elapsed since surgery (3.5 vs. 3.1 years, $p=0.36$) (Table 2). Compared to participants without sexual dysfunction, those with sexual dysfunction were more likely to have poor sleep ($p=0.002$), less likely to have had sex in the last year ($p=0.005$) more likely to have hot flashes ($p=0.002$), and less likely to be currently using systemic hormone therapy (HT) ($p = 0.002$) or testosterone ($p=0.02$). Women with and without sexual dysfunction endorsed similar utilization of vaginal HT and non-hormonal therapies (including phytoestrogens, black cohosh, gabapentin, clonidine, primrose or acupuncture) for hot flashes. Sexual dysfunction was associated with higher reporting of depression ($p<0.001$) and anxiety ($p = 0.001$). Utilization of psychiatric medications appeared to be higher in the group reporting sexual dysfunction (40.6 vs. 30.8%) with borderline significance ($p = 0.054$). The mean FSFI score was 20.3 for those with sexual dysfunction who did not score in the depression range and 19.8 for those with sexual dysfunction who not score in the anxiety range.

Participants with either hot flashes (aOR 1.92, 95% CI 1.23-3.02) or depression (aOR 2.4, 95% CI 1.4-4.1) had an approximately two-fold greater risk of sexual dysfunction after adjusting for age at the time of survey, sexual activity in the last year, and psychiatric medication use.

To determine risk factors for those with the most severe sexual dysfunction in our cohort, we compared those with scores in the lowest quartile (FSFI ≤ 14) to those with sexual dysfunction in the upper quartiles ($14 < \text{FSFI} \leq 26.55$), as well as with those without sexual dysfunction (FSFI >26.55) (Table 3). Women with scores in the lowest FSFI quartile were more likely to be obese (25.8% vs. 17.4%, $p = 0.049$) and have depression (50.3 vs. 30.1%, $p<0.001$) as compared with women with less severe sexual dysfunction. After adjusting for confounders, (age at the time of survey, sex in the last year), depressive symptoms were significantly associated with the most severe sexual dysfunction (aOR 2.1, 95% CI 1.3-3.5, $p=0.002$). Conversely, high educational attainment (college graduate or above) was associated with lower odds of experiencing the most severe sexual dysfunction (aOR 0.5, 95% CI 0.3-0.9, $p=0.013$).

Those with severe sexual dysfunction were more likely to be older– both at the time of survey completion (mean age 47.6 years vs. 45.5 years, $p=0.03$) and at the time of RRSO (43.8 years vs. 42.5 years, $p=0.03$). Those with the worst sexual dysfunction were more likely to have poor sleep ($p=0.04$), less likely to have had sex in the last year ($p<0.001$) more likely to have hot flashes ($p=0.003$), and less likely to be currently using systemic hormone therapy (HT) ($p = 0.002$) or testosterone ($p=0.03$) compared to those without sexual dysfunction. They were also significantly more likely to endorse depression (<0.001) and anxiety (<0.001) symptoms as compared with those without sexual dysfunction, but psychiatric medication use was similar ($p = 0.06$).

Sexual Function Domain Analysis

Each FSFI domain was analyzed separately (Table 4) to determine risk factors for psychological (Desire, Arousal, Satisfaction) versus physical aspects (Lubrication, Orgasm, Pain) of sexual dysfunction. Both depression ($p < 0.001$) and anxiety ($p = 0.03$) were associated with low Desire scores, even after adjusting for sexual activity. Low Arousal was associated with age at the time of survey, obesity and with depression, however none of these risk factors remained significant after adjusting for sexual activity. Low Satisfaction was associated with depressive symptoms (adjusted OR 1.7, 95% CI 1.1-2.6, $p = 0.02$). Current vaginal HT use was associated with improved Lubrication (adjusted OR 0.3, 95% CI 0.1-0.9, $p = 0.03$) and Orgasm scores (adjusted OR 0.2, 95% CI 0.1-0.8, $p = 0.02$).

Subgroup Analysis

A restricted analysis of participants who were under the age of 50 with no history of cancer was performed to exclude the effect of somatic age and cancer therapies on sexual dysfunction. Consistent with findings from the total cohort, sexual dysfunction was associated with older age at the time of survey (42.5 $\pm$ 4.3 years, $p = 0.01$), older age at RRSO (40.5 vs. 38.9 years, $p = 0.01$), and fewer participants who had sex in the last year (93% vs. 100%, $p = 0.048$) within this subgroup. Women under 50 without cancer who had sexual dysfunction were more likely to have hot flashes (71.2% vs. 46%, $p = 0.001$), have poor sleep (98.2% vs. 82.1%, $p = 0.003$) and less likely to be using systemic hormone therapy (41.9% vs. 66%, $p = 0.003$). Depressive ($p = 0.001$) and anxious ($p = 0.007$) symptoms were both significantly associated with sexual dysfunction, as seen in the total RRSO cohort, with borderline significance with psychiatric medication use (39.3% vs. 24.5%, $p = 0.05$).

DISCUSSION

To our knowledge, this is the largest study to date to examine risk factors for sexual dysfunction in a cohort of BRCA mutation carriers following RRSO. The overwhelming majority of participants who underwent RRSO reported sexual dysfunction (77.3%) - a finding that was both higher than BRCA carriers who had not pursued RRSO (36.7%), and general population prevalence estimates (40%)¹⁶. In those who had undergone RRSO, our data suggest that while several factors contribute to sexual dysfunction, depression has the strongest and most consistent association, irrespective of antidepressant therapy. This association was independent of age, timing of most recent sexual activity, HT use, cancer history, and educational attainment, suggesting that depression is an important, potentially under-recognized and undertreated component in sexual function following RRSO.

Interestingly, the removal of the ovaries and loss of ovarian hormones appeared to have a significant negative effect on sexual dysfunction, as demonstrated by our comparison of sexual dysfunction in those who had undergone RRSO with those who had yet to undergo surgery. While the data on the effects of premature surgical menopause on depressive symptoms is limited, some studies have found that surgically menopausal women have more depressive symptoms than those who were naturally menopausal²³. A prospective study comparing 257 premenopausal women undergoing hysterectomy without oophorectomy with 57 women undergoing hysterectomy with oophorectomy demonstrated a higher rate of

depressive symptoms in women with oophorectomy during a 3-year follow-up period²⁴. Given the higher rate of depressive symptoms in women who had undergone RRSO as compared with those who had not yet undergone RRSO (13 vs. 10%, $p = 0.003$), it is certainly possible that premature surgical menopause might contribute to depression.

The relationship between depression and sexual dysfunction has been described as “bi-directional”^{20, 21}. As such, it is often challenging to determine causality as depression may cause sexual dysfunction or vice versa, and treatment for one may improve or contribute to worsening symptoms of the other. Sexual dysfunction is highly prevalent among patients with depression.^{17–19} One meta-analysis found that depression increased the risk of sexual dysfunction (OR 1.7, 95% CI 1.1–2.8), and sexual dysfunction increased the risk of depression (OR 3.1, 95% CI 1.7–5.9)²¹. Furthermore, treatment of depression with certain antidepressants is associated with sexual dysfunction^{16, 22}. In this study, while reported use of psychiatric medication use was high amongst those with sexual dysfunction (40.6%), use appeared to be a borderline risk factor for sexual dysfunction.

Our study also noted a reduction in sexual dysfunction amongst those taking hormone therapy (HT) after RRSO. HT following RRSO in premenopausal BRCA carriers without breast cancer is a viable treatment option for menopausal symptoms²⁵. Limited data exists on the safety of HT in this population, however a recent systematic review from 2016 reported that the risks of subsequent cancer following HT are small²⁶. In an observational study by Rebbeck et al, there was no elevated breast cancer risk with the use of HT following RRSO (HR 0.37, 95% CI = 0.14–0.96)²⁵. Given its benefits concerning menopausal symptoms, HT is not an unreasonable treatment option in BRCA carriers who have undergone prophylactic oophorectomy²⁶. There are mixed data regarding the benefit of HT on sexual dysfunction in this population. In a cross-sectional study, HT reduced vasomotor symptoms in women post-RRSO, but did not improve sexual functioning²⁸. Nonetheless, Finch and colleagues demonstrated that HT use improved both symptoms of vaginal dryness and sexual discomfort among oophorectomized patients¹⁰. Several studies support the use of testosterone in addition to estrogen therapy for surgically menopausal women for improvement of sexual function and wellbeing^{29, 30}. While there was a reduced odds of sexual dysfunction associated with testosterone use in this current study (OR 0.3, 95% CI 0.1–0.8), the overall number of participants who used testosterone in this study was small ($n = 14$), so it is difficult to draw any substantial conclusions about the added benefit of testosterone.

HT has also been shown to reduce rates of depression and anxiety following bilateral oophorectomy in the non-BRCA population^{31, 32}. This study showed no association between systemic HT use and depression or anxiety, although it may be underpowered to detect this association given the limited utilization of HT. If the increased rate of depressive symptoms was due to the loss of ovarian hormones, one would expect that HT would be associated with a reduced rate of these symptoms, however this was not observed in this study. Due to the small percentage of women reporting HT use of any kind, we may not be able to draw strong associations between depression and HT. It is possible that if prevalence of HT use was higher, we might be able to observe the beneficial effect of these medications on depressive symptoms. However, as 24.6% of our participants who had undergone RRSO

were using systemic HT, and HT was associated with a 50% risk reduction in sexual dysfunction, HT may be an underutilized therapy that could confer substantial benefits.

We hypothesized that specific disorders of sexual function (i.e. hypoactive sexual desire disorder, sexual arousal disorder, sexual pain disorders and orgasmic disorders) would have unique risk factor associations. Depression appeared to have a negative impact on all aspects of sexual function, Desire, Arousal, Lubrication, Orgasm, Satisfaction and Pain, both physical and psychological. After adjusting for sexual activity in the last year, depression still associated with low Desire and Satisfaction, psychological aspects of sexual function. Obesity was associated with low Arousal, Lubrication, Orgasm and Pain domain scores, both psychological and physical aspects of sexual function. This finding is consistent with published reports in obese populations^{33–35} Our study also demonstrated a relationship between a history of cancer and Lubrication, Orgasm, and Pain, the physical aspects of sexual function which is consistent with previous studies that have demonstrated the negative impact that cancer diagnoses and treatments (chemotherapy, radiation and surgery) have on sexual function^{36, 37}. These findings strengthen an understanding of the facets of the sexual response that may be connected to modifiable risk factors.

Strengths and Limitations

The major strengths of this study are its relatively large sample size and use of a validated female sexual dysfunction questionnaire. The BRCA mutation carrier population will be one of the most at-risk populations to undergo salpingo-oophorectomy, given what is known about the negative consequences of removing the ovaries, both in premenopausal and postmenopausal women. We used a novel approach to identify risk factors for the lowest FSFI scores, which would inform clinicians regarding who may be at risk for the worst sexual dysfunction. We also had available 40 BRCA mutation positive women that had yet to undergo RRSO and had the opportunity to compare FSFI scores before and after surgery, be it a small comparison group. This was a convenience sample recruited from an academic referral hospital for women with high-risk mutations and from a national website, these results may not be generalizable to *all* BRCA carriers; however, these findings are important to clinicians counseling patients who are presenting for RRSO consultation. Limitations of this study include its cross-sectional nature, thus causality cannot be determined. This study utilized self-reported patient surveys obtained through online questionnaire, and not by a trained interviewer. Thus, quality of life symptoms such as depression and anxiety are self-reported and may not reflect clinically diagnosed disorders. Furthermore, the relationship between depression and sexual dysfunction is confounding and are difficult to completely disentangle. With regard to partner status, we were able to capture current relationship status (married or in a domestic partnership) through our questionnaire, however did not obtain data on multiple partners or partner status before or after RRSO or after diagnosis of BRCA mutation. This would certainly be a consideration in prospective data collection. Additionally, due to incomplete medication data, we were unable to report on specific dosing of hormone therapy or specific types of testosterone use. As there were 235 women who did not complete the FSFI portion, there may be selection bias with respect to the women who chose to answer these questions. However, as our analysis demonstrated, the women who completed the FSFI were overall similar to the women who did not. While the

study is cross-sectional in nature, the size of cohort and ability to analyze subgroups allowed for evaluation sexual dysfunction. A prospective longitudinal study following sexual functioning before and after surgery would be the ideal next step to understanding the role of surgery on sexual dysfunction. We are currently following the 40 women who had yet to undergo surgery in this study in order to compare their pre-surgery and post-surgery scores.

CONCLUSIONS

Sexual dysfunction is highly prevalent in women with BRCA mutations following RRSO. Depression is a significant risk factor for sexual dysfunction and may be both under-recognized and/or undertreated. Any provider, in oncology, gynecology or primary care, should be highly vigilant about assessing both sexual dysfunction and depression in women who have had their ovaries removed. As HT has not been associated with negative long-term consequences in this population (albeit with limited data), HT may be of benefit in the management of sexual dysfunction and should be considered in those without breast cancer. Educating women about the possible sexual side effects of surgical risk reduction is imperative and addressing sexual dysfunction and its risk factors is paramount to improving quality of life after RRSO in patients with BRCA mutations.

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Figure 1.

Patient flow diagram

Abbreviations: RRSO = Risk Reducing Salpingo-Oophorectomy, FSFI = Female Sexual Function Index

Table 1

Baseline characteristics of total cohort

	RRSO (Total n = 764)			p-value [‡]	No RRSO (n = 40)	p-value [*]
	Completed FSFI (n = 529)	Did not complete FSFI (n = 235)				
Age at the time of survey, years	46.5±7.5	50.2±9.0		<0.001	35±4.0	<0.001
Age at time of RRSO, years	43.4±7.4	46.9±10.9		<0.001	NA	NA
White race	484 (91.5%)	208 (88.5%)		0.19	37 (92.5%)	0.68
College graduate	444 (83.9%)	187 (79.6%)		0.29	37 (92.5%)	0.13
Married or in domestic partnership	474 (89.6%)	148 (63%)		<0.001	31 (77.5%)	0.56
Sex in the last year	472 (89.2%)	113 (48.1%)		<0.001	36 (90%)	0.06
Obesity (BMI ≥ 30 kg/m ²)	103 (19.5%)	47 (20.0%)		0.65	7 (17.5%)	0.70
Cancer history	219 (41.4%)	107 (45.5%)		0.10	0 (0%)	<0.001
Prior chemotherapy	126 (23.8%)	56 (23.8%)		0.59	0 (0%)	<0.001
Prior hysterectomy	294 (55.6%)	104 (44.3%)		0.047	0 (0%)	<0.001
Prior mastectomy	363 (68.6%)	138 (58.7%)		0.15	17 (42.5%)	<0.001
FSFI score	19.2±8.8	NA		NA	27.9±4.0	<0.001
Sexual dysfunction (FSFI ≤ 26.55)	409 (77.3%)	NA		NA	11 (27.5%)	<0.001
Poor sleep (PSQI ≥ 5)	308 (58.2%)	170 (72.3%)		0.02	22 (55%)	0.92
Case depression	69 (13%)	30 (12.8%)		0.23	4 (10%)	0.003
Case anxiety	80 (15.1%)	27 (11.5%)		0.93	15 (37.5%)	0.15
Hot flashes	347 (65.6%)	111 (47.2%)		0.15	11 (27.5%)	<0.001

Abbreviations: RRSO = risk-reducing salpingo-oophorectomy, FSFI = Female Sexual Function Index, NA = Not Applicable, BMI = body mass index, PSQI = Pittsburgh sleep quality index

Data presented as mean ± SD or n (%)

^{*} P-value comparing RRSO vs. non-RRSO group, calculated from Chi-squared, Mann-Whitney U or Fisher's exact tests as appropriate[‡] P-value comparing those who completed FSFI vs. those who had not, calculated from Chi-squared and Mann-Whitney U tests as appropriate

Table 2

Risk factors for sexual dysfunction after RRSO

	Sexual dysfunction (n = 409)	No sexual dysfunction (n = 120)	Unadjusted OR (95% CI)	p-value*
FSFI summary score	16.1±7.4	29.9±3.3	NA	<0.001
Age at the time of survey, years	46.8±7.5	45.5±7.3	1.02 (1.0–1.05)	0.10
Age at time of RRSO, years	43.6±7.6	42.5±6.3	1.02 (0.99-1.05)	0.15
Time elapsed since surgery, years	3.5±4.0	3.1±4.1	1.03 (0.97-1.1)	0.36
Premenopausal at the time of RRSO	198 (48.4%)	59 (49.2%)	0.8 (0.3-2.2)	0.67
White race	372 (91%)	112 (93.3%)	0.7 (0.3-1.6)	0.41
College graduate	343 (83.9%)	101 (84.2%)	1.0 (0.6-1.8)	0.93
Married or in domestic partnership	371 (90.7%)	103 (85.8%)	1.7 (0.9-3.1)	0.11
Sex in the last year	355 (86.8%)	117 (97.5%)	0.1 (0.01-0.4)	0.005
Obesity (BMI ≥ 30 kg/m ²)	82 (20%)	21 (17.5%)	1.2 (0.7-2.0)	0.55
Cancer history	166 (40.6%)	53 (44.2%)	0.9 (0.6-1.3)	0.48
Prior chemotherapy	99 (24.2%)	27 (22.5%)	1.1 (0.6-1.7)	0.63
Prior hysterectomy	219 (53.5%)	75 (62.5%)	0.7 (0.5-1.1)	0.09
Prior mastectomy	283 (69.1%)	80 (66.7%)	1.1 (0.7-1.7)	0.73
Aromatase inhibitor use [†]	37 (9%)	7 (5.8%)	1.6 (0.7-3.7)	0.27
Poor sleep (PSQI >5)	249 (60.9%)	59 (49.2%)	3.8 (1.6-9.5)	0.002
Hot flashes	284 (69.4%)	63 (52.5%)	1.95 (1.3-3.0)	0.002
Systemic HT use [‡]	88 (21.5%)	42 (35%)	0.5 (0.3-0.8)	0.002
Vaginal HT use [‡]	32 (7.8%)	8 (6.7%)	1.2 (0.5-2.7)	0.67
Testosterone use [‡]	6 (1.5%)	8 (6.7%)	0.3 (0.1-0.8)	0.02
Non-hormonal treatment for hot flashes [‡]	19 (4.6%)	9 (7.5%)	0.9 (0.4-2.0)	0.72
Depression [§]	150 (36.7%)	20 (16.7%)	2.8 (1.6-4.7)	<0.001
Anxiety [§]	131 (32%)	20 (16.7%)	2.4 (1.4-4.1)	0.001
Psychiatric medication use	166 (40.6%)	37 (30.8%)	1.5 (1.0-2.4)	0.054

Abbreviations: RRSO = risk-reducing salpingo-oophorectomy, FSFI = female sexual function index, NA = not-applicable BMI = body mass index, PSQI = Pittsburgh sleep quality index, HT = hormone therapy

Data presented as mean ± SD or n(%)

* p value calculated from Chi-squared, Student's t-test, Mann-Whitney U or Fisher's exact tests as appropriate

[†] Percentage of patients who reported current use of these medications

[‡] Percentage of patients who reported ever using these medications

[§] Case and borderline depression and anxiety included

^{||} Antidepressant or anxiolytic use included

Table 3
Comparison of lowest FSFI quartile with upper FSFI quartiles and with those with no sexual dysfunction

	Lowest FSFI Quartile (FSFI (n = 133))	Upper FSFI Quartiles (FSFI >14, 26.55) (n = 276)	p-value*	No sexual dysfunction (FSFI >26.55) (n = 120)	p-value*
FSFI summary score	7.0±4.4	20.5±3.5	<0.001	29.9±3.3	<0.001
Age at the time of survey, years	47.6 ± 7.8	46.4±7.3	0.12	45.5±7.3	0.03
Age at time of RRSO, years	43.8±7.2	43.1±6.2	0.08	42.5±6.3	0.03
Time elapsed since surgery (years)	3.7±4.2	3.4±3.9	0.38	3.1±4.1	0.15
Premenopausal at the time of RRSO	63 (47.4%)	135 (48.9%)	0.11	59 (49.2%)	0.15
White race	119 (89.5%)	253 (91.7%)	0.47	112 (93.3%)	0.28
College graduate	103 (77.4%)	240 (87%)	0.006	101 (84.2%)	0.18
Married or in domestic partnership	116 (87.2%)	224 (81.2%)	0.151	103 (85.8%)	0.75
Sex in the last year	91 (68.4%)	264 (95.7%)	<0.001	117 (97.5%)	<0.001
Obesity (BMI ≥ 30 kg/m ²)	34 (25.6%)	48 (17.4%)	0.049	21 (17.5%)	0.12
Cancer history	57 (42.9%)	109 (39.5%)	0.52	53 (44.2%)	0.83
History of chemotherapy	33 (24.8%)	66 (23.9%)	0.98	27 (22.5%)	0.86
History of hysterectomy	71 (53.4%)	148 (53.6%)	0.98	75 (62.5%)	0.16
History of mastectomy	99 (74.4%)	184 (66.7%)	0.25	80 (66.7%)	0.35
Current aromatase inhibitor use	13 (9.8%)	24 (8.7%)	0.72	7 (5.8%)	
Poor sleep (PSQI >5)	90 (67.7%)	159 (56.5%)	0.53	59 (49.2%)	0.04
Hot flashes	95 (71.4%)	189 (68.5%)	0.21	63 (52.5%)	0.003
Current systemic HT use	24 (18%)	64 (23.2%)	0.21	42 (35%)	0.002
Current vaginal HT use	11 (8.3%)	21 (7.6%)	0.84	8 (6.7%)	0.64
Testosterone use ever	1 (0.8%)	5 (4.4%)	0.43	8 (6.7%)	0.03
Non-hormonal treatment for hot flashes [‡]	5 (3.8%)	14 (5.1%)	0.65	9 (7.5%)	0.57
Depression [‡]	67 (50.3%)	83 (30.1%)	<0.001	20 (16.7%)	<0.001
Anxiety [‡]	51 (38.3%)	80 (29%)	0.06	20 (16.7%)	<0.001
Psychiatric med use [§]	56 (42.1%)	110 (39.9%)	0.66	37 (30.8%)	0.06

Abbreviations: FSFI = Female Sexual Function Index, RRSO = risk-reducing salpingo-oophorectomy, BMI = body mass index, PSQI = Pittsburgh Sleep Quality Index, HT = hormone therapy

Data presented as mean±SD or n(%)

* p value calculated from Chi-squared, Student's t-test, Mann-Whitney U or Fisher's exact tests as appropriate

[†] Percentage of patients who reported ever using systemic hormonal therapy

[‡] Case and borderline depression and anxiety included

[§] Antidepressant or anxiolytic use included

Table 4

Significant risk factors for lowest quartile FSFI (<14) domain scores

N =409 (Lowest quartile n = 133, Upper quartiles n= 276)	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI) †	p-value
Desire				
Depression [‡]	2.5 (1.7-3.6)	<0.001	2.2 (1.5-3.3)	<0.001
Anxiety [‡]	1.6 (1.0-2.3)	0.03	1.7 (1.1-2.5)	0.02
Arousal				
Age at time of survey *	1.03 (1.0-1.1)	0.04	1.01 (0.98-1.1)	0.47
Obesity (BMI ≥ 30 kg/m ²)	2.3 (1.1-4.6)	0.02	2.0 (1.0-4.0)	0.06
Depression [‡]	1.7 (1.0-2.9)	0.03	1.5 (0.9-2.5)	0.12
Lubrication				
Age at time of survey	1.06 (1.03-1.1)	<0.001	1.01 (0.98-1.04)	0.72
Obesity (BMI ≥ 30 kg/m ²)	1.9 (1.2-2.9)	0.004	1.4 (0.8-2.3)	0.27
College graduate	0.6 (0.4-0.9)	0.02	0.7 (0.4-1.3)	0.23
Cancer history	1.8(1.2-2.6)	0.002	1.1 (0.7-1.7)	0.84
Current systemic HT use	0.4 (0.2-0.7)	0.001	0.7 (0.4-1.2)	0.17
Current vaginal HT use	0.4 (0.2-1.0)	0.048	0.3 (0.1-0.9)	0.03
Depression [‡]	1.6 (1.1-2.3)	0.018	1.1 (0.7-1.8)	0.61
Orgasm				
Age at time of survey *	1.06 (1.03-1.1)	<0.001	1.0 (0.97-1.03)	0.93
College graduate	0.6 (0.4-0.9)	0.02	0.6 (0.4-1.1)	0.12
Obesity (BMI ≥ 30 kg/m ²)	1.7 (1.1-2.6)	0.02	1.2 (0.7-2.0)	0.575
Cancer history	1.9 (1.3-2.8)	<0.001	1.1 (0.7-1.8)	0.61
Current systemic HT use	0.4 (0.2-0.7)	0.001	0.7 (0.4-1.2)	0.20
Current vaginal HT use	0.3 (0.1-0.9)	0.03	0.2 (0.1-0.8)	0.02
Depression [‡]	1.6 (1.1-2.3)	0.02	1.2 (0.7-1.9)	0.55
Satisfaction				
Age at time of survey *	1.03 (1.0-1.05)	0.03	0.98 (0.96-1.01)	0.27
Depression [‡]	1.9 (1.3-2.9)	0.001	1.7 (1.1-2.6)	0.02
Pain				
Age at time of survey *	1.06 (1.03-1.1)	<0.001	1.0 (0.97-1.04)	0.76
College graduate	0.6 (0.4-1.0)	0.049	0.7 (0.4-1.2)	0.21
Obesity (BMI ≥ 30 kg/m ²)	1.7 (1.1-2.6)	0.014	1.2 (0.7-2.2)	0.44
Cancer history	1.7 (1.2-2.4)	0.003	0.95 (0.6-1.5)	0.83
Hot flashes	0.7 (0.5-1.00)	0.049	0.6 (0.4-1.0)	0.06
Night sweats	0.6 (0.4-0.8)	0.003	0.5 (0.3-0.8)	0.003
Current systemic HT use	0.4 (0.3-0.7)	0.001	0.7 (0.4-1.3)	0.24

N =409 (Lowest quartile n = 133, Upper quartiles n= 276)	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI) [†]	p-value
Depression [‡]	1.5 (1.0-2.1)	0.04	1.1 (0.7-1.7)	0.73

Abbreviations: FSFI = Female Sexual Function Index, BMI = body mass index, HT = hormone therapy

* Age analyzed continuously

[†] Adjusted for sexual activity in the last year

[‡] Case and borderline depression and anxiety included.