WOMEN'S SEXUAL HEALTH

Hormone Levels and Sexual Functioning After Risk-Reducing Salpingo-Oophorectomy

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ABSTRACT

Introduction: Women after risk-reducing salpingo-oophorectomy (RRSO) can have impaired sexual functioning, but whether there is an association between hormone levels and sexual functioning is unclear.

Aim: To determine whether hormone levels are associated with sexual functioning in women after RRSO.

Methods: This is a retrospective cohort study of 198 sexually active and 91 inactive women after RRSO. Participants completed the Sexual Activity Questionnaire, questionnaires concerning hormone replacement therapy (HRT), quality of life, care from partner, body image, and comorbidity and provided blood samples. Associations between sexual functioning scores and covariates were examined by linear regression. Variables associated with sexual activity were examined by logistic regression.

Main Outcome Measures: Associations with sexual pleasure and sexual discomfort scores were expressed by multivariable regression coefficients and associations with sexual activity were expressed by odds ratios.

Results: None of the hormone levels were associated with sexual pleasure in contrast to age ($P = .032$), current use of systemic HRT ($P = .002$), and more care form partner ($P < .001$). Increased free androgen index ($P = .016$), more care from partner ($P = .017$), systemic HRT ($P = .002$), and no history of cardiovascular disease ($P = .001$) were associated with less sexual discomfort. The odds ratio of being sexually active increased with younger age, no breast cancer, better quality of life, and more care from partner.

Conclusions: Our results indicate that other factors than hormone levels are important for sexual functioning, although systemic HRT can have a positive impact on sexual functioning in women who have undergone RRSO. Testosterone therapy could improve women's sexual functioning after RRSO; however, the inverse association between free androgen levels and sexual discomfort should be addressed in future studies. **Johansen N, Liavaag AH, Mørkird L, Michelsen TM. Hormone Levels and Sexual Functioning After Risk-Reducing Salpingo-Oophorectomy. Sex Med 2018;6:143–153.**

Key Words: *BRCA1* Gene; *BRCA2* Gene; Ovariectomy; Hormones; Sexuality; Hormone Replacement Therapy

INTRODUCTION

Ovarian cancer is the most lethal of gynecologic malignancies. Of women with breast cancer susceptibility (BRCA) gene mutations, up to 60% develop epithelial ovarian cancer.[1] Risk-reducing salpingo-oophorectomy (RRSO) lowers the risk of epithelial ovarian cancer by 80% in BRCA mutation carriers,[2] and the surgery is recommended at 35 to 45 years of age. RRSO implies removal of healthy organs from young, healthy individuals, and any side effects need particular attention. Most of a woman's estrogen and approximately half her testosterone are produced by the ovaries.[3] Hence, RRSO substantially decreases the levels of these hormones.[4] Women who undergo RRSO before natural menopause experience menopausal symptoms. Vasomotor symptoms and dyspareunia can be alleviated by hormone replacement therapy (HRT), but HRT does not seem to improve sexual pleasure.[5,6] Testosterone treatment has been shown to be effective in postmenopausal women with sexual dysfunction,[7–9] but the results are conflicting concerning

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the associations between sex hormone levels and sexual functioning.[4,8,10,11] Other investigators have examined sexual functioning after RRSO using the Sexual Activity Questionnaire with sexual pleasure and sexual discomfort as the main variables.[5,12] In a recent study, we found that women after RRSO had less sexual pleasure and more sexual discomfort than women from the general population. Davis et al[8] found a correlation between testosterone levels and sexual response in women; however, a 2014 review concluded that the obtained plasma androgen levels could not predict response to therapy.[13]

Several factors, especially psychosocial aspects, can affect sexual functioning.[14–16] Basson et al[17] suggested that female sexual functioning follows a complex and non-linear model that includes emotional intimacy, sexual stimuli, and relational satisfaction. Hence, variations in psychosocial conditions might overshadow a possible relation between hormone levels and sexual functioning, and other studies have not made these adjustments. Knowledge about associations between hormone levels and sexual functioning is limited and could be useful in the treatment of sexual dysfunction after RRSO.

Aims

Our primary aim was to examine the association between hormone levels and sexual functioning after adjustment for psychosocial and inter-relational aspects. Secondary aims were to investigate the association between systemic HRT and sexual functioning scores and to determine whether hormone levels were associated with sexual activity.

METHODS

Study Sample

The study sample was based on a group of women who had undergone RRSO. The indication for the preventive surgery was inherited increased risk of breast and ovarian cancer, and all women had genetic counseling before surgery at the Norwegian Radium Hospital (Oslo, Norway). We did not have access to the women's BRCA mutation status. 503 women were identified through surgical records from 3 Norwegian university hospitals. The women were invited to participate by mailed questionnaires; 361 responded and gave informed consent (response rate = 72%) after 1 reminder. 56 participants were excluded because of missing, incomplete, or inconsistent answers, and another 13 were excluded because of missing or unreliable dates of RRSO. Only the women who had RRSO in 1990 or later were included in the study. Sexually active women were those who had answered "yes" and sexually inactive women were those who answered "no" to the question, "Are you engaged in any sexual relation at the moment?" 198 sexually active women had a partner and were included as sexually active and 91 sexually inactive women were included (Figure 1). Except for date of birth and date of RRSO, we had no information about the non-responders. The women provided demographic and health-related information by filling out specific questionnaires. Blood samples for hormone analyses were collected at their general practitioners' offices.

Measures and Questionnaires

Except for age at survey and age at RRSO, all data were self-reported. Paired relationship was defined as being married or having an intimate relationship. High education was defined as more than 12 years. Systemic HRT was defined as preparations with systemic effect. Cardiovascular disease was defined as coronary heart disease or cerebral stroke. Obstructive pulmonary symptoms were defined as persistent cough and/or obstructive breathing. Musculoskeletal disorders or persistent symptoms were defined as osteoporosis, fibromyalgia, osteoarthritis, other musculoskeletal disorders, or persistent musculoskeletal pain or stiffness for at least 3 months.

The Sexual Activity Questionnaire is validated[18,19] and includes relationship status, reasons for sexual abstinence, and sexual functioning. Sexual pleasure consists of 6 items: "sex is important," "do enjoy sexual activity," "desire to have sex," "feel satisfied with sex," "frequency of sexual activity," and "satisfied with the frequency of sexual activity." The sexual discomfort

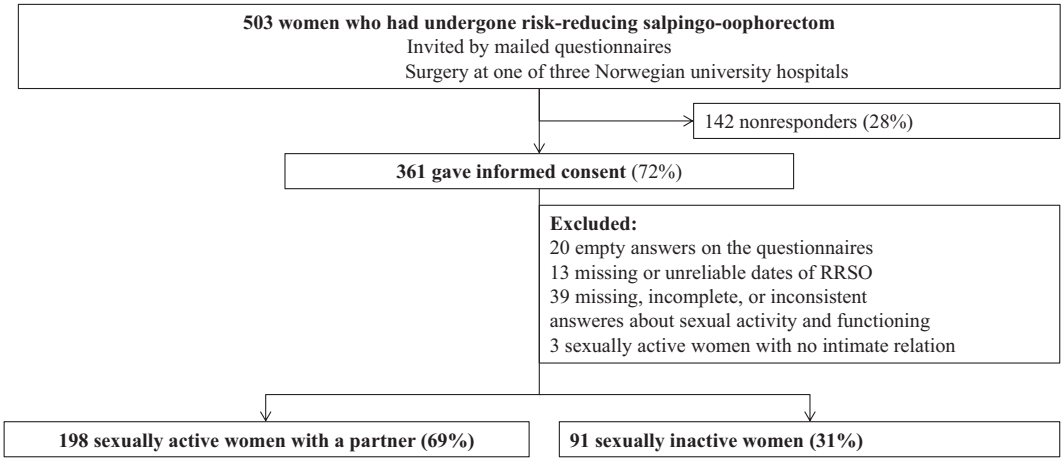

Figure 1. Inclusion of participants. RSSO = risk-reducing salpingo-oophorectomy.

score is the sum of "vaginal dryness" and "pain or discomfort during penetration." All items were rated on a Likert scale from "not at all" (0) to "very much" (3); higher scores meant more pleasure and discomfort, respectively. Internal consistency estimated by Cronbach α was 0.91 for the sexual pleasure score and 0.85 for the sexual discomfort score.

Body image is the sum of 5 general items: "feeling self-conscious about your appearance," "dissatisfied with your appearance when dressed," "finding it difficult to look at yourself naked," "avoiding people because of the way you felt about your appearance," and "feeling dissatisfied with your body." Items were rated on a scale from "not at all" (0) to "very much" (3); a higher score reflected poorer body image.[20] The internal consistency was 0.86.

Quality of life was measured using the mean score of 2 questions—"How would you rate your overall physical condition during the past week?" and "How would you rate your overall quality of life during the past week?"—from the European Organization and Treatment of Cancer QLQ-C30.[21] The 2 questions were rated on a Likert scale from "very poor" (0) to "excellent" (6). The scores were transformed to a 0 to 100 scale, in which higher scores meant a better quality of life. The internal consistency was 0.91.

Care from partner was assessed using the care construct from the Intimate Bond Measure,[22] from which 12 questions concerning care from partner were rated on a scale from "not at all" (0) to "very much" (3); a higher sum score meant more care from partner. The internal consistency was 0.95. The Hospital Anxiety and Depression Scale was used to assess depression and anxiety by 7 items for each subscale. This tool is validated and has good psychometric properties.[23,24] Internal consistency was 0.77 and 0.83 for the depression and anxiety scores, respectively.

Measurements of Hormone Levels

Blood samples were collected at general practitioners' offices for analyses of thyroxine, thyrotropin, estradiol, luteinizing hormone, follicle-stimulating hormone, sex hormone-binding globulin (SHBG), testosterone, and dehydroepiandrosterone sulfate (DHEAS). Serum was separated and instantly cooled for delivery to the Hormone Department at Aker University Hospital (Oslo, Norway) on the same day. Thyrotropin and thyroxine were measured by a Cenatur chemiluminescent assay with acridinium ester (Bayern, Tarrytown, NY, USA). Estradiol, follicle-stimulating hormone, and luteinizing hormone were measured by DELFIA (Wallac, Turku, Finland), an immunofluoroassay kit with analytical coefficient of variation less than 10%, less than 4%, and less than 5%, respectively. Testosterone was measured by a kit from Orion Diagnostica (Espoo, Finland) using a competitive radioimmunoassay with a coefficient of variation less than 14%. DHEAS and SHBG were measured with the Immulite 2000 (Diagnostic Products Corporation, Los Angeles, CA, USA). DHEAS was measured using a competitive luminescence immunoassay with a coefficient of variation less than 7%. The free androgen index was calculated as total testosterone $\times$ 100/SHBG and represents the unbound fraction of total testosterone.[25]

Statistics

Continuous variables were described by medians and interquartile ranges, and differences between groups were calculated by the Mann-Whitney U-test. Categorical variables were described by numbers and proportions, and group differences were calculated by Pearson χ^2 test. Internal consistency of the questionnaire scales was measured by Cronbach α. The hormone levels had right-skewed distributions; therefore, all analyses were performed with Box-Cox transformed values. The outcomes of the statistical tests were essentially the same using the untransformed values; for simplicity, only the analyses of untransformed hormone values are presented. Correlations were assessed by Spearman ρ.

We performed multivariable linear regressions with sexual functioning scores as dependent variables, and the independent variables were chosen as follows. We performed bivariate analyses to examine the associations between each independent variable and the dependent variable, in which the covariates that were associated with the dependent variable with P values higher than .20 were kept for multivariable linear regression (enter model). To provide a solid model, we proceeded with a backward model with only the statistically significant independent variables as covariates. Cases were excluded list-wise if values were missing. No heteroscedasticity was present. Associations with sexual activity were examined by logistic regression. Tukey fences with a factor of 1.5 were used to identify outliers of the hormone levels. All outliers were examined, and none were excluded because they were consistent with the medical histories, and no technical errors were indicated. Despite significant correlations between the free androgen index and DHEAS (Spearman $\rho = 0.56$) and between follicle-stimulating hormone and luteinizing hormone (Spearman $\rho = 0.70$), the variance inflation factor calculated by SPSS (IBM Corp, Armonk, NY, USA) indicated no substantial multicollinearity in the final regression models.

We examined the biological relevance of the statistically significant associations by testing the Gowans criterion (equivalent to effect size).[26] This is an attempt to make a threshold for the effect size based on a shift from the central tendency in a reference population. Modified SDs of sexual pleasure and sexual discomfort scores were estimated. These new SDs were calculated from the part of their distribution that followed the course of a Gaussian distribution. Modified SDs were calculated from the distribution between the 5th and 95th and between the 50th and the 95th percentiles of sexual pleasure and discomfort scores, respectively. We calculated the shift of the dependent variable caused by a 1-SD change in a covariate. Then, the Gowans criterion was applied: if this shift exceeded 1/4 SD of the dependent variable, then the association was interpreted as

biologically relevant. All statistical analyses were performed by SPSS 21. Significance level was set to 0.05 and all tests were 2-tailed.

Ethics Approval

The study was approved by the Regional Committee for Medical and Health Research Ethics South East of Norway in September 2012 (REC number 2012/1165).

RESULTS

Study Sample

The sexually active women were younger than the inactive women (median = 53 and 58 years, respectively; $P = .003$). More sexually active women were in paired relationships ($P < .001$), had no history of breast cancer ($P = .001$), and were current users of systemic HRT ($P = .004$). The sexually active women reported a lower body image score (representing a better body image; $P = .010$), better quality of life ($P < .001$), and more care from partner ($P < .001$). Further, the sexually active women had less cardiovascular disease, less musculoskeletal complaints, and less depression and anxiety symptoms (Table 1).

Sexual Pleasure Score

The sexual pleasure score ranged from 0 to 18. The median was 11 (1st quartile = 7, 3rd quartile = 14). The modified SD was estimated to be 5.60. The regression model with sexual pleasure score as the dependent variable explained 25.9% of the variance of the sexual pleasure score.

Covariates Associated With Sexual Pleasure Score

None of the hormone levels were significantly associated with the sexual pleasure score. In the final multivariable analysis, age ($P = .032$), current use of systemic HRT ($P = .002$), and more care from partner ($P < .001$) were positively associated with an increased sexual pleasure score (Table 2). Of these variables, systemic HRT and more care from partner were interpreted as biologically relevant (Supplementary Table). We performed a multivariable linear regression analysis of the sexual pleasure score by including all independent variables in a backward model with unaltered analyses (data not shown).

Sexual Discomfort Score

The sexual discomfort score ranged from 0 to 6. The median was 1 (1st quartile = 0, 3rd quartile = 3). The modified SD was estimated to be 2.37. The regression model explained 20.7% of the variation in discomfort score.

Covariates Associated With Sexual Discomfort Score

In the final multivariable analysis, increased free androgen index ($P = .016$), current use of systemic HRT ($P = .002$), more care from partner ($P = .017$), and no history of cardiovascular disease ($P = .001$) were significantly associated with less sexual discomfort (Table 3). Of these, current use of HRT and no history of cardiovascular disease were interpreted as biologically relevant (Table 3, Supplementary Table). We performed a multivariable linear regression analysis of the sexual discomfort score by including all independent variables in a backward model and obtained essentially the same results (data not shown).

Table 1. Demographics

	Sexually active (n = 198)	Sexually inactive (n = 91)	*P* value
Age (y), median (min–max)	53 (33–76)	58 (36–79)	.003*
Age at RRSO (y), median (min–max)	47 (31–70)	51 (33–76)	.004*
Time since RRSO (y), median (min–max)	5 (1–16)	6 (1–15)	.56*
High education (>12 y), n (%)	89 (45.2)	30 (33.3)	.059
Married or having an intimate relation, n (%)	198 (100)†	54 (60.7)	<.001
History of breast cancer, n (%)	35 (17.9)	33 (36.3)	.001
Current use of systemic HRT, n (%)	68 (39.1)	16 (20.5)	.004
Body image score, median (min–max)	0 (0–11)	1 (0–15)	.010*
Quality of life, median (min–max)	83.3 (16.7–100)	66.7 (0–100)	<.001*
Care from partner, median (min–max)	30 (6–36)	20 (1–36)	<.001*
Cardiovascular disease, n (%)	5 (2.6)	7 (8.2)	.035
Diabetes, n (%)	4 (2.1)	3 (3.5)	.50
Obstructive pulmonary symptoms, n (%)	29 (15.3)	15 (17.2)	.70
Musculoskeletal disorder or persisting symptoms, n (%)	105 (54.4)	60 (66.7)	.051
Depression score, median (min–max)	2 (0–15)	3 (0–15)	<.001*
Anxiety score, median (min–max)	4 (0–15)	6 (0–21)	<.001*

HRT = hormone replacement therapy; max = maximum; min = minimum; RRSO = risk-reducing salpingo-oophorectomy.
*By non-parametric Mann-Whitney U-test.
†The 3 sexually active women with missing information or without an intimate relationship were excluded.

Table 2. Associations with sexual pleasure score among sexually active women after RRSO (n = 198); linear regression with sexual pleasure score as the dependent variable

			Enter model		Backward model		Multivariable regression coefficient × $SD_{independent}/SD_{dependent}$
Covariates	Univariable regression coefficient, B (95% CI)	*P* value*	Multivariable regression coefficient, B (95% CI)	*P* value†	Multivariable regression coefficient, B (95% CI)	*P* value‡	
Estradiol	−2.65 (−8.56 to 3.25)	.38					
LH	0.037 (−0.015 to 0.089)	.16	−0.033 (−0.107 to 0.042)	.39			
FSH	0.018 (−0.008 to 0.043)	.17	0.029 (−0.009 to 0.068)	.13			
Total testosterone	−0.066 (−1.65 to 1.52)	.94					
DHEAS	0.040 (−0.368 to 0.448)	.85					
SHBG	−0.015 (−0.041 to 0.010)	.24					
Free androgen index§	0.262 (−0.115 to 0.640)	.17	0.193 (−0.243 to 0.63)	.38			
fT_4	−0.195 (−0.495 to 0.106)	.20					
TSH	0.008 (−0.637 to 0.652)	.98					
Age	0.024 (−0.055 to 0.103)	.54	0.072 (0.008–0.152)	.077	0.082 (−0.007 to 0.156)	.032	0.12‖
Education	0.240 (−1.07 to 1.56)	.72					
History of breast cancer	−1.37 (−3.06 to 0.325)	.11	−0.330 (−2.06 to 1.40)	.71			
Current use of systemic HRT	1.53 (0.172–2.89)	.028	2.08 (0.46–3.71)	.031	2.02 (0.72–3.32)	.002	0.36‖
Quality of life	0.060 (0.028–0.092)	<.001	0.038 (0.002–0.077)	.062			
Care from partner	0.316 (0.236–0.395)	<.001	0.271 (0.181–0.362)	<.001	0.290 (0.206–0.370)	<.001	0.38‖
Body image score	−0.158 (−0.448 to 0.132)	.28					
Cardiovascular disease	1.034 (−3.09 to 5.16)	.62					
Diabetes	−0.382 (−5.0 to 4.2)	.87					
Obstructive pulmonary symptoms	−1.221 (−3.08 to 0.64)	.20					
Musculoskeletal disorder or persisting symptoms	−0.97 (−2.28 to 0.34)	.15	0.327 (−1.03 to 1.68)	.63			
Depression score	−0.40 (−0.67 to −0.13)	.004	0.204 (−0.129 to 0.54)	.23			
Anxiety score	−0.339 (−0.54 to −0.141)	.001	−0.192 (−0.44 to 0.052)	.12			

DHEAS = dehydroepiandrosterone sulfate; FSH = follicle-stimulating hormone; fT_4 = free thyroxine; HRT = hormone replacement therapy; LH = luteinizing hormone; RRSO = risk-reducing salpingo-oophorectomy; TSH = thyrotropin.

*Based on bivariate linear regression.

†Based on enter model of linear regression.

‡Based on backward model of linear regression.

§Free androgen index = total testosterone × 100/SHBG.

‖According to Gowans' criterion, the association between a covariate and the sexual functioning score was interpreted as biologically relevant when a 1 SD change in the covariate resulted in a change in the value of the sexual functioning score of ≥ 0.25 of the SD of the latter.

Table 3. Associations with sexual discomfort score among sexually active women after RRSO (n = 198); linear regression with sexual discomfort score as the dependent variable

Covariates	Univariate regression coefficient, B (95% CI)	*P* value*	Enter model		Backward model		Multivariable regression coefficient × $SD_{independent}/SD_{dependent}$
			Multivariable regression coefficient, B (95% CI)	*P* value†	Multivariable regression coefficient, B (95% CI)	*P* value‡	
Estradiol	−0.661 (−3.26 to 1.93)	.62					
LH	−0.009 (−0.032 to 0.014)	.44					
FSH	0.008 (−0.003 to 0.019)	.17	0.009 (−0.003 to 0.020)	.15			
Total testosterone	−0.859 (−1.55 to −0.170)	.015	‖				
DHEAS	−0.279 (−0.454 to −0.104)	.002	−0.089 (−0.322 to 0.143)	.45			
SHBG	0.008 (−0.004 to 0.019)	.18	‖				
Free androgen index§	−0.261 (−0.424 to −0.098)	.002	−0.188 (−0.43 to 0.055)‖	.13	−0.230 (−0.42 to −0.043)	.016	0.17¶
fT_4	0.084 (−0.050 to 0.218)	.22					
TSH	−0.132 (−0.415 to 0.152)	.36					
Age	0.039 (0.006–0.073)	.021	0.002 (−0.039 to 0.043)	.93			
Education	−0.185 (−0.751 to 0.381)	.52					
History of breast cancer	0.821 (0.092–1.55)	.028	0.155 (−0.68 to 0.98)	.71			
Current use of systemic HRT	−1.24 (−1.82 to −0.657)	<.001	−0.71 (−1.43 to −0.005)	.052	−0.95 (−1.54 to −0.37)	.002	0.40¶
Quality of life	−0.019 (−0.033 to −0.005)	.010	−0.017 (−0.036 to −0.002)	.086			
Care from partner	−0.047 (−0.085 to −0.009)	.016	−0.043 (−0.086 to −0.001)	.046	−0.047 (−0.086 to −0.009)	.017	0.14¶
Body image score	0.059 (−0.066 to 0.184)	.35					
Cardiovascular disease	2.93 (1.204–4.65)	.001	3.66 (1.06–6.7)	.006	3.08 (1.32–4.9)	.001	1.3¶
Diabetes	1.37 (−0.59 to 3.33)	.17	#				
Obstructive pulmonary symptoms	−0.163 (−0.97 to 0.64)	.69					
Musculoskeletal disorder or persisting symptoms	0.73 (0.16–1.29)	.012	0.199 (−0.45 to 0.85)	.55			
Depression score	0.080 (−0.038 to 0.198)	.18	−0.042 (−0.209 to 0.126)	.62			
Anxiety score	0.114 (0.028–0.200)	.010	0.057 (−0.065 to 0.179)	.36			

DHEAS = dehydroepiandrosterone sulfate; FSH = follicle-stimulating hormone; fT_4 = free thyroxine; HRT = hormone replacement therapy; LH = luteinizing hormone; RRSO = risk-reducing salpingo-oophorectomy; TSH = thyrotropin.

*Based on bivariate linear regression.

†Based on enter model of linear regression.

‡Based on backward model of linear regression.

§Free androgen index = total testosterone × 100/SHBG.

‖For the multivariable analysis we chose to keep the free androgen index and neither total testosterone nor SHBG because the free androgen index is the estimate of the free and active proportion of total testosterone.

¶According to the Gowans criterion, the association between a covariate and the sexual functioning score was interpreted as biologically relevant when a 1-SD change in the covariate resulted in a change in the value of the sexual functioning score of at least 0.25 of the SD of the latter.

#Not applicable because few women had diabetes.

Variables Associated With Being Sexually Active

Among the hormone levels, increased free androgen index was associated with lower odds of being sexually active (odds ration [OR] = 0.75, 95% CI = 0.56−0.99). Older age (OR = 0.92, 95% CI = 0.86−0.98), history of breast cancer (OR = 0.283, 95% CI = 0.097−0.82), and increased anxiety score (OR = 0.81, 95% CI = 0.68−0.96) were associated with decreased odds of being sexually active, whereas more care from partner (OR = 1.13, 95% CI = 1.06−1.20) was associated with increased odds of being sexually active after adjusted analyses (Table 4). Of the 91 sexually inactive women, 27 women explained their sexual inactivity with problems related to their partner. The most common partner-related reason for not being sexually active was that the partner had no interest in sex (n = 15).

DISCUSSION

No hormone levels were associated with sexual pleasure, whereas an increase in free androgen index of at least 2.2 units (SD = 1.24) showed a biologically relevant inverse association with sexual discomfort. Current use of systemic HRT and more care from partner were positively associated with more sexual pleasure, and use of systemic HRT and no history of cardiovascular disease were associated with less sexual discomfort.

In accordance with Aziz et al,[4] who examined associations between sex hormone levels and sexuality before and after bilateral salpingo-oophorectomy, we found no association between estrogen levels and sexual functioning. In contrast, Woods et al[27] found a positive association between higher estrogen levels and more sexual motivation. In the latter study, the women underwent natural menopause, which includes considerable estrogen fluctuations, and might not be comparable to women after RRSO. However, androgens rather than estrogen have been linked to sexual drive and arousal, and testosterone therapy is effective as treatment of sexual dysfunction in postmenopausal women.[7−9,28] In the present study, a 2.2-unit increase of free androgen index levels showed a biologically relevant association with less sexual discomfort. This increase corresponds to the

Table 4. Variables associated with being sexually active in women after RRSO who lived in paired relationship (n = 252): logistic regression with being sexually active (yes vs no) as the dependent variable

	Unadjusted OR (95% CI)*	*P* value	Adjusted OR (95% CI)*,†	*P* value
Estrogen	49 (0.08−29 170)	.23		
LH	1.01 (0.99−1.04)	.33		
FSH	1.00 (0.99−1.01)	.97		
Total testosterone	0.48 (0.26−0.88)	.018	¶	
DHEAS	1.00 (0.83−1.21)	.97		
SHBG	1.01 (0.99−1.02)	.46		
Free androgen index‡	0.87 (0.75−1.01)	.063	0.75 (0.56−0.99)	.043
fT_4	1.03 (0.90−1.18)	.70		
TSH	0.87 (0.68−1.12)	.28		
Age	0.94 (0.91−0.98)	.001	0.92 (0.86−0.98)	.009
Education	1.60 (0.85−3.02)	.15	1.00 (0.38−2.60)	.99
History of breast cancer	0.316 (0.164−0.61)	.001	0.283 (0.097−0.82)	.021
Current use of systemic HRT	2.89 (1.27−6.6)	.012	2.06 (0.56−7.6)	.28
Quality of life	1.03 (1.01−1.04)	<.001	1.01 (0.98−1.04)	.68
Care from partner	1.11 (1.07−1.16)	<.001	1.13 (1.06−1.20)	<.001
Body image score‖	0.88 (0.79−0.98)	.020	0.93 (0.77−1.11)	.39
Cardiovascular disease	0.316 (0.082−1.22)	.095	0.42 (0.049−3.61)	.43
Diabetes	1.08 (0.12−9.84)	.95		
Obstructive pulmonary symptoms	1.33 (0.52−3.40)	.55		
Musculoskeletal disorder or persisting symptoms	0.52 (0.27−0.99)	.046	1.33 (0.48−3.71)	.59
Depression score	0.83 (0.75−0.92)	<.001	1.10 (0.87−1.38)	.44
Anxiety score	0.83 (0.76−0.91)	<.001	0.81 (0.68−0.96)	.018

DHEAS = dehydroepiandrosterone sulfate; FSH = follicle-stimulating hormone; fT_4 = free thyroxine; HRT = hormone replacement therapy; LH = luteinizing hormone; OR = odds ratio; RRSO = risk-reducing salpingo-oophorectomy; TSH = thyrotropin.

*Odds ratio less than 1 indicates that when an independent variable increases, the probability of being sexually active is decreased.

†The selection of variables chosen to be controlled for in the adjusted analyses was done according to (i) which variables were significantly or nearly significantly associated with the dependent variable in the unadjusted analyses, (ii) exclusion of 1 variable in highly correlated bivariate pairs, and (iii) a priori knowledge of what could be relevant for the inclusion of a variable. Hence, we adjusted for TSH, free androgen index, LH, age, body image, education, quality of life, care from partner, history of breast cancer, and current use of systemic HRT.

‡Free androgen index = total testosterone × 100/SHBG.

‖A higher score on the body image scale represents a poorer body image.

¶Total testosterone was not kept for the multivariable analyses because the free androgen index is the estimate of the free and active proportion of circulating testosterone, and total testosterone is included in the calculation.

effect expected after testosterone therapy.[8,13] Testosterone therapy can increase genital vasocongestion and sensation[29]; therefore, an association between free androgen index and sexual discomfort is biologically plausible. In addition, testosterone can be converted to estrogens in the peripheral tissue and thereby exert an effect on sexual function. We found no association between androgen levels and sexual pleasure in the present study. Tucker et al[10] conducted a study on sexual functioning and androgens in women after RRSO, and they found no associations between androgens and sexual pleasure. In contrast, Davis et al[8] found positive correlations between androgen levels and number of satisfying sexual events, sexual desire, and orgasm. However, no adjustments were performed, and the correlations observed could represent the effect of testosterone treatment. Testosterone therapy is effective, but the effect on sexual functioning might not correspond with measured androgen levels.[8] This could explain in part why we found no significant associations between androgens and sexual functioning. In the United States, testosterone therapy is recommended for women with hypoactive sexual desire disorder. The treatment should be monitored to assess overuse and discontinued if no effect is observed after 6 months. Although short-term testosterone treatment is safe, there are no data available after 24 months,[13] and the safety in BRCA carriers has not been examined.

Our finding of an association between systemic HRT and more sexual pleasure seems contradictory to our previous study in which we included local and systemic preparations in the definition of HRT use.[6] Therefore, we reanalyzed the data from the present study, and the association between HRT use and sexual pleasure was no longer significant ($P = 0.14$; data not shown) when local and systemic preparations were included and thus in line with our previous findings.[6] This indicates that only systemic HRT has impact on sexual pleasure. However, Finch et al,[5] who conducted a longitudinal study on 114 BRCA mutation carriers who underwent RRSO, found that the decrease in sexual pleasure was not alleviated by HRT. Therefore, studies on the impact of HRT on sexual pleasure are divergent. However, in accordance with Finch et al,[5] we found that systemic HRT was associated with less sexual discomfort. If RRSO is performed at the recommended age, the surgery leads to menopause and can be associated with adverse effects.[5,6,30,31] The postmenopausal symptoms and adverse effects are decreased by systemic HRT.[5,30,31] Therefore, European and North American guidelines recommend that women after RRSO use systemic HRT until the age of natural menopause if they have no history of breast cancer.[32–35] However, fear of breast cancer was the most frequently reported reason for non-use among HRT-eligible women in the study of Challberg et al,[31] which is reasonable because these women had a high risk of breast cancer. Nevertheless, short-term HRT does not seem to increase the risk of breast cancer after RRSO[36] and is considered safe.[35] In addition to breast cancer, contraindications to systemic HRT include estrogen-sensitive tumors, undiagnosed vaginal bleeding or endometrial hyperplasia, venous thromboembolism, cardiovascular disease, severe hepatic disease, and porphyria cutanea tarda.[33,34] One participant in the present study had a history of myocardial infarction, and none had previous venous thromboembolism. We did not have detailed information about the other conditions, but these conditions are rare in women younger than the age of natural menopause. Therefore, we do not believe that contraindications to HRT other than breast cancer biased our analyses. The association between less discomfort and no history of cardiovascular disease is in accordance with previous literature[37]; however, the finding should be interpreted with caution because there were only 5 sexually active women who had a history of cardiovascular disease in our study sample.

In accordance with previous findings,[16] more care from partner was associated with increased sexual pleasure. It is noteworthy that this was the strongest association observed, and the findings indicate that the relationship between the woman and her partner is a more important determinant of sexual functioning than her hormone levels. This finding supports the Basson model, which states that female sexual functioning is considerably affected by numerous psychosocial issues: satisfaction with the relationship, self-image, and previous negative sexual experiences.[17]

Further, lower levels of free androgen index were associated with increased odds of being sexually active. This might seem counterintuitive because women with high levels of free androgen index had less sexual discomfort. However, the use of systemic HRT can decrease the free amount of testosterone by increasing SHBG.[38] Hence, this finding could be a result of residual confounding. Other variables associated with increased likelihood of being sexually active were younger age, no history of breast cancer, better quality of life, and more care from partner, all in accordance with previous reports.[14,15] A large proportion of women in the present study had a history of breast cancer owing to their genetic cancer susceptibility. Surgical treatment, chemotherapy, and antiestrogen treatment can negatively affect sexual functioning. Induction of premature menopause can induce an estrogen-deficient state that leads to hot flashes, lubrication difficulties, and changes in libido and thereby contribute to sexual inactivity. Vaginal dryness is the most common persisting postmenopausal symptom. Lorenz et al[39] conducted a study of how the vaginal complaints influenced the sexual activity of women who underwent RRSO. The women who were satisfied with their relationship continued to have sex despite severe vaginal symptoms, whereas the women with low relationship satisfaction became sexually inactive if they had vaginal complaints. The women after RRSO who were in paired relationships reported the same reasons for sexual inactivity as women in paired relationships from the general Norwegian population.[6]

Based on the present findings, we recommend that women who opt for RRSO receive realistic and proper preoperative

information of potential postoperative sexual side effects, are advised to use systemic HRT, and that the women with their partners are offered sexual counseling after the surgery.

Strengths and Limitations

Strengths of the present study are the sample size and the measurement of hormone levels. The high grade of explained variation of the regression models indicated an acceptable model fit. Women who undergo RRSO constitute a heterogeneous group with respect to breast cancer diagnosis and treatment. Yet, the Sexual Activity Questionnaire has been validated for healthy pre- and postmenopausal women, women with high risk of cancer, women with normal risk of cancer, and women who have been diagnosed with cancer.[19] There are some limitations. (i) The study does not have baseline measurements of sexual functioning scores, which could have provided a prospective follow-up, and causal relations could have been explored. (ii) Except for birth date and date of RRSO, the information about the participants was self-reported and can lead to recall bias. However, self-reporting of breast cancer has high sensitivity and specificity[40] in women from the general population and might be even higher in women after RRSO. (iii) The lack of a control group could be considered a limitation. Yet, in our previous controlled study of the present cohort, the RRSO group reported less sexual pleasure and more sexual discomfort than did controls from the general population.[6] In the present study, we aimed to determine underlying factors that could be associated with sexual functioning scores in the RRSO group; therefore, we believe the study design is appropriate to answer our research questions. (iv) Given the retrospective design, the women who volunteered to participate might be those with better or worse sexual functioning and, hence, subject to selection bias, which could have any direction. (v) Sexual functioning was evaluated by the Sexual Activity Questionnaire that lacks questions concerning arousal and orgasm. Nevertheless, we included psychosocial scales and hormone levels as covariates, which we believe provided good models to explain the sexual functioning scores. However, we cannot disregard that hormone levels could have impact on a domain of sexual functioning that is not measured by the Sexual Activity Questionnaire. (vi) Testosterone therapy was not included in the questionnaire. (vii) The free androgen index was used to estimate free testosterone levels. The Södergård equation assesses the quantity of total testosterone that is bound to albumin and is a preferred method[25]; however, albumin was not measured in our study. (viii) We did not have access to the women's BRCA mutation status. Nevertheless, because we studied associations with sexual side effects after the prophylactic surgery in *BRCA1* and *BRCA2* mutation carriers, and because the RRSO procedure does not depend on the *BRCA* mutation status, we do not believe that the type of BRCA mutation was determinative in the analyses. (ix) Breast cancer treatment negatively affects female sexual functioning,[41] but we did not have access to detailed information about cancer treatment. (x) Parity can influence sexual functioning[42]; parous women have reported less sexual satisfaction than nulliparous women. However, we did not have access to parity information. (xi) A prior study found that female sexual functioning was significantly impaired if the women's partners had erectile dysfunction,[43] but the erectile function of the women's partners was not covered by the Sexual Activity Questionnaire. (xii) The immunometric method used to measure sex hormone levels enables cross-reaction with other steroids and can overestimate hormone levels. A more sensitive method is mass spectrometry, but this method was not available in our laboratory.

CONCLUSIONS

Women after RRSO reported better sexual functioning if they received more care from their partner and were current users of systemic HRT. No hormone levels were associated with sexual pleasure. Therefore, the present study indicates that other factors than hormone levels determine sexual functioning after RRSO. The inverse relation between free androgen index and sexual discomfort should be addressed in future studies.

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SUPPLEMENTARY DATA

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