GYNECOLOGY

Sexual functioning more than 15 years after premenopausal risk-reducing salpingo-oophorectomy

Lara Terra, MD; Maarten J. Beekman, MD; Ellen G. Engelhardt, PhD; Bernadette A. M. Heemskerk-Gerritsen, PhD; Marc van Beurden, MD, PhD; Jeanine E. Roeters van Lennep, MD, PhD; Helena C. van Doorn, MD, PhD; Joanne A. de Hullu, MD, PhD; Eleonora B. L. Van Dorst, MD; Constantijne H. Mom, MD, PhD; Brigitte F. M. Slangen, MD, PhD; Katja N. Gaarenstroom, MD, PhD; Lizet E. van der Kolk, MD, PhD; J. Margriet Collée, MD; Marijke R. Wevers, MD, PhD; Margreet G. E. M. Ausems, MD, PhD; Klaartje Van Engelen, MD, PhD; Irma van de Beek, MD, PhD; Lieke P. V. Berger, MD; Christi J. van Asperen, MD, PhD; Encarna B. Gomez Garcia, MD, PhD; Angela H. E. M. Maas, MD, PhD; Maartje J. Hooning, MD, PhD; Neil K. Aaronson, PhD; Marian J. E. Mourits, MD, PhD; Flora E. van Leeuwen, PhD

BACKGROUND: Women with a *BRCA1/2* pathogenic variant are advised to undergo premenopausal risk-reducing salpingo-oophorectomy after completion of childbearing, to reduce their risk of ovarian cancer. Several studies reported less sexual pleasure 1 to 3 years after a premenopausal oophorectomy. However, the long-term effects of premenopausal oophorectomy on sexual functioning are unknown.

OBJECTIVE: This study aimed to study long-term sexual functioning in women at increased familial risk of breast or ovarian cancer who underwent a risk-reducing salpingo-oophorectomy either before the age of 46 years (premenopausal group) or after the age of 54 years (postmenopausal group). Subgroup analyses were performed in the premenopausal group, comparing early (before the age of 41 years) and later (at ages 41—45 years) premenopausal risk-reducing salpingo-oophorectomy.

STUDY DESIGN: Between 2018 and 2021, 817 women with a high familial risk of breast or ovarian cancer from an ongoing cohort study were invited to participate in our study. Because of a large difference in age in the study between the premenopausal and postmenopausal salpingo-oophorectomy groups, we restricted the comparison of sexual functioning between the groups to 368 women who were 60 to 70 years old at completion of the questionnaire (226 in the premenopausal group and 142 in the postmenopausal group). In 496 women with a premenopausal risk-reducing salpingo-oophorectomy, we compared the sexual functioning between women in the early premenopausal group (n=151) and women in the later premenopausal group (n=345). Differences between groups were analyzed using multiple regression analyses, adjusting for current age, breast cancer history, use of hormone replacement therapy, body mass index, chronic medication use (yes or no), and body image.

RESULTS: Mean times since risk-reducing salpingo-oophorectomy were 20.6 years in the premenopausal group and 10.6 years in the postmenopausal group ($P<.001$). The mean age at questionnaire completion was 62.7 years in the premenopausal group, compared with 67.0 years in the postmenopausal group ($P<.001$). Compared with 48.9% of women in the postmenopausal group, 47.4% of women in the premenopausal group were still sexually active ($P=.80$). Current sexual pleasure scores were the same for women in the premenopausal group and women in the postmenopausal group (mean pleasure score, 8.6; $P=.99$). However, women in the premenopausal group more often reported substantial discomfort than women in the postmenopausal group (35.6% vs 20.9%; $P=.04$). After adjusting for confounders, premenopausal risk-reducing salpingo-oophorectomy was associated with substantially more discomfort during sexual intercourse than postmenopausal risk-reducing salpingo-oophorectomy (odds ratio, 3.1; 95% confidence interval, 1.04—9.4). Moreover, after premenopausal risk-reducing salpingo-oophorectomy, more severe complaints of vaginal dryness were observed (odds ratio, 2.6; 95% confidence interval, 1.4—4.7). Women with a risk-reducing salpingo-oophorectomy before the age of 41 years reported similar pleasure and discomfort scores as women with a risk-reducing salpingo-oophorectomy between ages 41 and 45 years.

CONCLUSION: More than 15 years after premenopausal risk-reducing salpingo-oophorectomy, the proportion of sexually active women was comparable with the proportion of sexually active women with a postmenopausal risk-reducing salpingo-oophorectomy. However, after a premenopausal risk-reducing salpingo-oophorectomy, women experienced more vaginal dryness and more often had substantial sexual discomfort during sexual intercourse. This did not lead to less pleasure with sexual activity.

Key words: BRCA1, BRCA2, BRCA pathogenic variants, ovariectomy, sexual discomfort, sexual pleasure, surgical menopause, vaginal dryness

Introduction

Risk-reducing salpingo-oophorectomy (RRSO) is performed to prevent ovarian or tubal cancer in women with a high familial risk, such as *BRCA1/2* pathogenic variant (PV) carriers. RRSO is advised after completion of childbearing, preferably at ages 35 to 40 years for *BRCA1* PV carriers and at ages 40 to 45 years for *BRCA2* PV carriers.[1] RRSO induces immediate menopause, which may result in short-term and long-term morbidity, such as decreased psychosexual functioning.

Reduced circulating estrogen levels because of menopause result in vulvovaginal atrophy, which may predispose to microtraumata when vaginal penetration occurs.[2] Up to 69% of postmenopausal women report vulvovaginal atrophy, with an increasing prevalence with a longer duration of menopause.[3—8] Hormone replacement therapy (HRT) may not alleviate symptoms[9] and is often not recommended in *BRCA* PV carriers because of the risk of breast cancer.

Several studies have examined the effect of RRSO on sexual functioning.[10]

Cite this article as: Terra L, Beekman MJ, Engelhardt EG, et al. Sexual functioning more than 15 years after premenopausal risk-reducing salpingo-oophorectomy. Am J Obstet Gynecol 2023;228:440.e1-20.

0002-9378

https://doi.org/10.1016/j.ajog.2022.11.1289

AJOG at a Glance

Why was this study conducted?

The uptake of risk-reducing salpingo-oophorectomy is very high. Sexual functioning can have a major effect on the quality of life. The long-term effects of premenopausal oophorectomy on sexual functioning are unknown.

Key findings

Women with a premenopausal risk-reducing salpingo-oophorectomy experience more discomfort during sexual intercourse and experience more vaginal dryness than women with a postmenopausal risk-reducing salpingo-oophorectomy more than 15 years after surgical menopause. Sexual pleasure is similar in women with a premenopausal and a postmenopausal risk-reducing salpingo-oophorectomy.

What does this add to what is known?

This study has provided information on long-term sexual functioning after premenopausal risk-reducing salpingo-oophorectomy.

Most showed that, shortly after RRSO, women experienced more discomfort and less pleasure with sexual activity.[11−14] However, this difference was not observed 6 years after RRSO.[15] It is possible that women developed coping mechanisms or explored practical solutions, in the years after RRSO, to be able to still be sexually active. Previous studies had several methodological limitations; age at study inclusion and age at RRSO varied widely, and adjustment for confounding factors (ie, breast cancer history and HRT use) was performed inconsistently. In addition, there are no long-term data on the effect of the duration of menopause on sexual functioning.

This study aimed to investigate the effect of a premenopausal RRSO on sexual functioning after at least 10 years. To overcome the limitations in previous research, we selected a large study cohort of women currently aged 55 years or older with a high familial risk of breast or ovarian cancer. We compared women who underwent a premenopausal RRSO (≤45 years) with women who underwent a postmenopausal RRSO (>54 years), and we performed subgroup analyses according to age at premenopausal RRSO, breast cancer history, and HRT use.

Materials and Methods

Patient selection and recruitment

The participants were Dutch women participating in the HARMOny study[16] (ClinicalTrials.gov; file number NCT03835793): a multicenter cross-sectional study, nested in a cohort of women at high familial risk of breast or ovarian cancer.[17,18] The study design and procedures have been described previously.[16] Briefly, between 2018 and 2021, we invited women to participate in a study assessing the long-term effects of RRSO on cardiovascular disease, bone health, cognition, and quality of life. The eligibility criteria included a high familial risk of breast or ovarian cancer, current age of ≥55 years, and having undergone RRSO either before the age of 45 years or after the age of 54 years. The exclusion criteria were ovarian cancer, metastatic disease, and therapy-induced menopause >5 years before RRSO. Breast cancer was not an exclusion criterion. Women were recruited from all Dutch university medical centers and the Netherlands Cancer Institute (NKI). The study has been approved by the institutional review board of the NKI.

Study assessments

Women were asked to complete a questionnaire on general health, cancer-specific outcomes, and medical treatments, including the use of HRT (never, former, or current use) and alternatives for HRT (eg, herbal supplements, cognitive behavioral therapy, or exercise). The questionnaire extensively addressed menopausal symptoms, including vaginal dryness, and body image (Supplementary Table 1).[19]

Sexual Activity Questionnaire

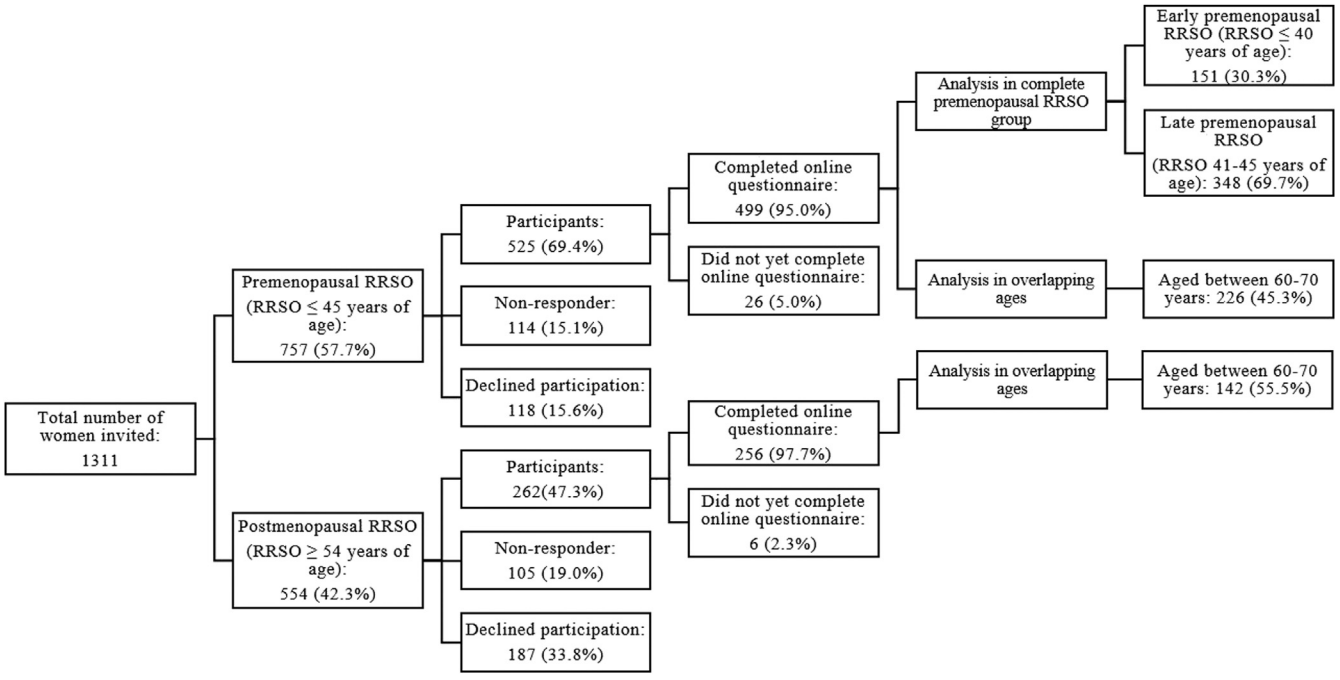
We assessed sexual functioning using the Sexual Activity Questionnaire (SAQ) (Supplementary Table 1).[20] The SAQ is a validated questionnaire[21,22] and consists of 3 parts. The first part assesses whether a woman is currently sexually active; those who are not sexually active complete the second part on reasons for sexual inactivity (Supplementary Table 3). Sexually active women complete the third part, which assesses several aspects of sexual function: pleasure, desire, satisfaction, vaginal dryness, penetration pain, and frequency of intercourse. We specifically asked women to report noncoital intercourse and masturbation. The questionnaire employs a 4-point Likert scale ("very much," "somewhat," "a little," or "not at all"). A composite score was calculated for "pleasure" (range, 0−18), "discomfort" (range, 0−6), and "habit" (ie, frequency of habitual sexual activity: range, 0−3).[20,22]

Statistical analyses

The differences in characteristics between the premenopausal and the postmenopausal RRSO groups were evaluated using the χ^2 test or the Fisher exact test for categorical data and independent samples t test for continuous data.

The association between the timing of RRSO and the various endpoints was analyzed using multiple linear regression for the SAQ pleasure score and multiple logistic regression for the SAQ discomfort score, the SAQ habit score, vaginal dryness, and pain with intercourse, yielding regression coefficients and odds ratios (ORs) with accompanying 95% confidence intervals (CIs). We created dichotomous variables for the discomfort score and the severity of vaginal dryness, comparing no discomfort or some discomfort (discomfort score of ≤2) with substantial discomfort (discomfort score of ≥3) and no vaginal dryness or somewhat vaginal dryness (score of ≤3) with substantial vaginal

FIGURE 1
Participant flowchart



Number of participants enrolled, nonresponders, and number of women who declined participation. We have sent out regular reminders to women to complete the online questionnaire. First, we compared women with a premenopausal RRSO with women with a postmenopausal RRSO, and second, we compared within the premenopausal RRSO group women with an early premenopausal RRSO with women with a later premenopausal RRSO.

RRSO, risk-reducing salpingo-oophorectomy.

Terra. Sexual functioning following premenopausal salpingo-oophorectomy. Am J Obstet Gynecol 2023.

dryness (score of ≥4). The postmenopausal RRSO group was used as the reference group. We adjusted for age at questionnaire completion and breast cancer history as potential confounders. Last, we included HRT, body mass index, hysterectomy (yes or no), preventive mastectomy (yes or no), chronic medication use (yes or no), and body image in our multiple regression analyses. A variable was removed from the model if the *P* value for its association with the outcome in the multivariate model was >.10. Because of collinearity between the variable "timing of RRSO" (premenopausal or postmenopausal RRSO) and "years since RRSO," we performed regression analyses with "timing of RRSO" as an independent variable. Subsequently, we performed sensitivity analyses with "years since RRSO."

In addition, we performed stratified analyses by breast cancer history and, within the premenopausal RRSO group, by age at RRSO (≤40 years vs 41−45 years), breast cancer history, and HRT use. For all statistical analyses, Stata (version 15.0; StataCorp LLC, College Station, TX) was used. *P* values of <.05 were considered statistically significant.

Results

Participation

Overall, 787 women gave informed consent (response rate, 60.0%), of whom 525 were in the premenopausal RRSO group (RRSO at ≤45 years of age) and 262 were in the postmenopausal RRSO group (RRSO at ≥55 years of age) (Figure 1). In the premenopausal RRSO group, 15.6% of women declined participation compared with 33.8% of women in the postmenopausal RRSO group.

Participant characteristics

In the complete study population, the mean age at questionnaire completion was 60.0 years in the premenopausal group, compared with 70.2 years in the postmenopausal group (*P*<.001) (Table 1). Compared with the postmenopausal RRSO group, women in the premenopausal group more often had a partner (72.9% vs 83.7%; *P*=.001) and were more often sexually active (39.3% vs 57.6%; *P*<.001). These differences could be largely explained by the older age of the postmenopausal RRSO group at questionnaire completion; with advancing age, the percentage of sexually active women decreased (Figure 2). Because women in the premenopausal RRSO group were substantially younger than women in the postmenopausal RRSO group, we restricted the comparison of sexual functioning between these groups to 368 women who were 60 to 70 years old at completion of the questionnaire (226 in the premenopausal group vs 142 in the postmenopausal group). Within all 496 women with a premenopausal RRSO, we compared sexual

TABLE 1
Characteristics of study participants

Patient characteristics	Entire study population		Women aged 60–70 y	
	Premenopausal RRSO (n=499)	Postmenopausal RRSO (n=256)	Premenopausal RRSO (n=226)	Postmenopausal RRSO (n=142)
Age at questionnaire completion, mean (SD)	60.0 (3.5)	70.2 (4.3)[a]	62.7 (2.5)	67.0 (2.1)[a]
Age at RRSO, mean (SD)	41.7 (2.8)	58.4 (3.6)[a]	42.1 (2.5)	56.5 (1.9)[a]
Time since RRSO, mean (SD)	18.3 (4.1)	11.9 (3.0)[a]	20.6 (3.3)	10.6 (1.9)[a]
Pathogenic genetic variants[b]				
BRCA1 germline mutation	241 (49.2%)	75 (29.4%)[a]	112 (49.6%)	39 (27.5%)[a]
BRCA2 germline mutation	96 (19.6%)	95 (37.3%)[a]	43 (19.0%)	51 (28.9%)[a]
Established noncarrier	153 (31.2%)	96 (33.3%)	70 (31.0%)	51 (28.9%)
Breast cancer (yes)	293 (59.0%)	166 (65.1%)	135 (59.7%)	82 (58.2%)
Breast cancer before RRSO	235 (84.8%)	146 (91.3%)[a]	104 (80.6%)	72 (91.1%)[a]
Breast cancer after RRSO	42 (15.2%)	14 (8.8%)[a]	25 (19.4%)	7 (8.9%)[a]
Treatment of breast cancer				
Surgery	284 (97.6%)	159 (98.8%)	132 (97.1%)	80 (98.8%)
Chemotherapy	222 (76.3%)	86 (52.4%)[a]	97 (48.7%)	51 (42.9%)
Radiotherapy	182 (62.5%)	95 (59.0%)	86 (63.2%)	54 (66.7%)
Endocrine therapy	106 (36.4%)	53 (32.9%)	41 (30.2%)	29 (35.8%)
Prophylactic mastectomy (yes)[c]	300 (62.1%)	84 (34.6%)[a]	140 (61.9%)	48 (33.8%)[a]
HRT use				
Current user	26 (5.2%)	2 (0.8%)[a]	14 (6.2%)	1 (0.7%)[a]
Past user	101 (20.0%)	27 (10.5%)[a]	46 (20.4%)	11 (7.7%)[a]
Never user	332 (66.5%)	210 (82.0%)[a]	146 (64.6%)	118 (83.1%)[a]
HRT duration in years, mean (SD)	2.2 (4.5)	1.4 (3.3)	2.1 (4.4)	1.6 (3.9)
Type of HRT				
Tibolone	37 (29.1%)	2 (6.9%)	1 (0.4%)	0 (0.0%)
Estradiol or progestogen	30 (23.6%)	0 (0.0%)	13 (5.8%)	0 (0.0%)
Estradiol only	11 (8.7%)	2 (6.9%)	7 (3.1%)	1 (0.7%)
Vaginal estrogen	2 (1.6%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
Unknown	47 (37.0%)	25 (86.2%)	204 (90.3%)	141 (99.3%)
BMI, mean (SD)	26.5 (5.0)	25.8 (4.5)	26.6 (5.2)	26.2 (5.0)
Hysterectomy (Yes)[d]	69 (16.2%)	53 (28.5%)[a]	43 (19.3%)	28 (19.7%)
Body image (EORTC-BR23), mean (SD)[e]	13.5 (18.3)	7.2 (11.3)[a]	19.6 (17.0)	9.0 (13.1)[a]
Chronic medication (yes)[f]	217 (43.5%)	139 (54.3%)[a]	124 (54.9%)	70 (49.3%)

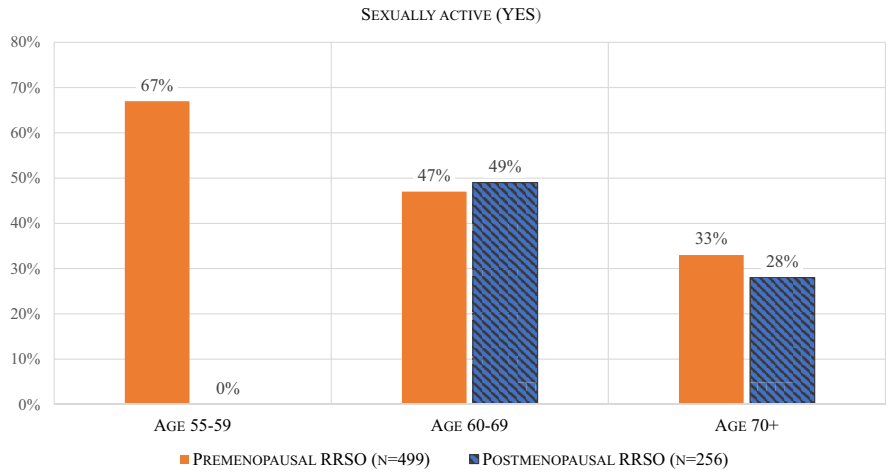
Additional characteristics of the study population are provided in Supplemental Table 2.

BMI, body mass index; *EORTC-BR23*, European Organization for Research and Treatment of Cancer Breast Cancer-Specific Questionnaire; *HRT*, hormone replacement therapy; *RRSO*, risk-reducing salpingo-oophorectomy; *SD*, standard deviation.

[a] *P* value of <.05. Groups were compared using independent samples *t* test, chi-square test, or Fisher exact test; [b] All participants had a high familial risk of ovarian cancer. All women were tested for pathogenic variants, not all women had a *BRCA1/2* mutation. Established noncarriers included women from BRCA1/2 families who tested negative and women from a breast or ovarian cancer family who tested negative for the pathogenic variants tested in the Netherlands; [c] Prophylactic mastectomy: bilateral or contralateral; [d] In the Netherlands, a hysterectomy is not standard of care when performing RRSO; [e] European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire[19] (questions 9–12), with higher scores indicating more problems with body image (range, 0–100); [f] Chronic medication use: any medication taken daily for cardiovascular risk factors, cardiovascular disease, or chronic disease.

Terra. Sexual functioning following premenopausal salpingo-oophorectomy. Am J Obstet Gynecol 2023.

FIGURE 2
Proportion of sexually active women by age at study



Age 55 to 59 years: 267 women with premenopausal RRSO, of whom 180 were sexually active, and no woman with postmenopausal RRSO; age 60 to 70 years: 226 women with premenopausal RRSO, of whom 107 were sexually active, and 142 women with postmenopausal RRSO, of whom 70 were sexually active; age ≥71 years: 6 women with premenopausal RRSO, of whom 2 were sexually active, and 114 women with postmenopausal RRSO, of whom 32 were sexually active.

RRSO, risk-reducing salpingo-oophorectomy.

Terra. Sexual functioning following premenopausal salpingo-oophorectomy. Am J Obstet Gynecol 2023.

functioning between women in the early premenopausal group (n=151) and women in the later premenopausal group (n=345). Results from analyses of the complete study population are provided in Supplementary Tables 5, 6 and Figure S1.

Of women aged 60 to 70 years, the mean times since RRSO were 20.6 years in the premenopausal group and 10.6 years in the postmenopausal group (Table 1). This difference is inherent to the inclusion criteria for the study. The mean age at questionnaire completion was 62.7 years in the premenopausal group vs 67.0 years in the postmenopausal group ($P<.001$). Compared with 63.8% of women in the postmenopausal RRSO group, 69.0% of women in the premenopausal RRSO group carried a *BRCA1/2* PV ($P=.40$). Compared with 58.2% of women in the postmenopausal group, 59.7% of women in the premenopausal RRSO group had a history of breast cancer ($P=.73$). Breast cancer treatment did not differ between the groups. HRT was more often prescribed to women in the premenopausal RRSO group (29.1%) than women in the postmenopausal RRSO group (9.2%) ($P<.001$). The duration of HRT use was similar in both groups (mean, 1.9 years).

Sexual activity and sexual functioning in women aged 60 to 70 years

In women aged 60 to 70 years, there was no difference in sexual activity between the groups (47.4% in the premenopausal RRSO group vs 48.9% in the postmenopausal RRSO group; $P=.80$). Among women who were sexually active (n=176), the mean pleasure score was 8.6 (standard deviation [SD], 3.7) in the premenopausal RRSO group vs 8.6 (SD, 3.0) in the postmenopausal group ($P=.80$) (Figure 3, A). Answers to individual questions of the pleasure score are shown in Supplementary Figure 3. Sexually active women with a premenopausal RRSO had slightly higher discomfort scores than sexually active women with a postmenopausal RRSO (2.0 [SD, 1.9] and 1.5 [SD, 1.6], respectively; $P=.07$), and women with a premenopausal RRSO more often had substantial discomfort than women with a postmenopausal RRSO (35.6% vs 20.9%, respectively; $P=.04$) (Figure 3, A and B). After adjustment for confounders, premenopausal RRSO was significantly associated with substantial discomfort during sexual intercourse (OR, 3.1; 95% CI, 1.04−9.4) (Table 2). The association between the mean pleasure score and the different discomfort scores can be found in Supplementary Figure 4.

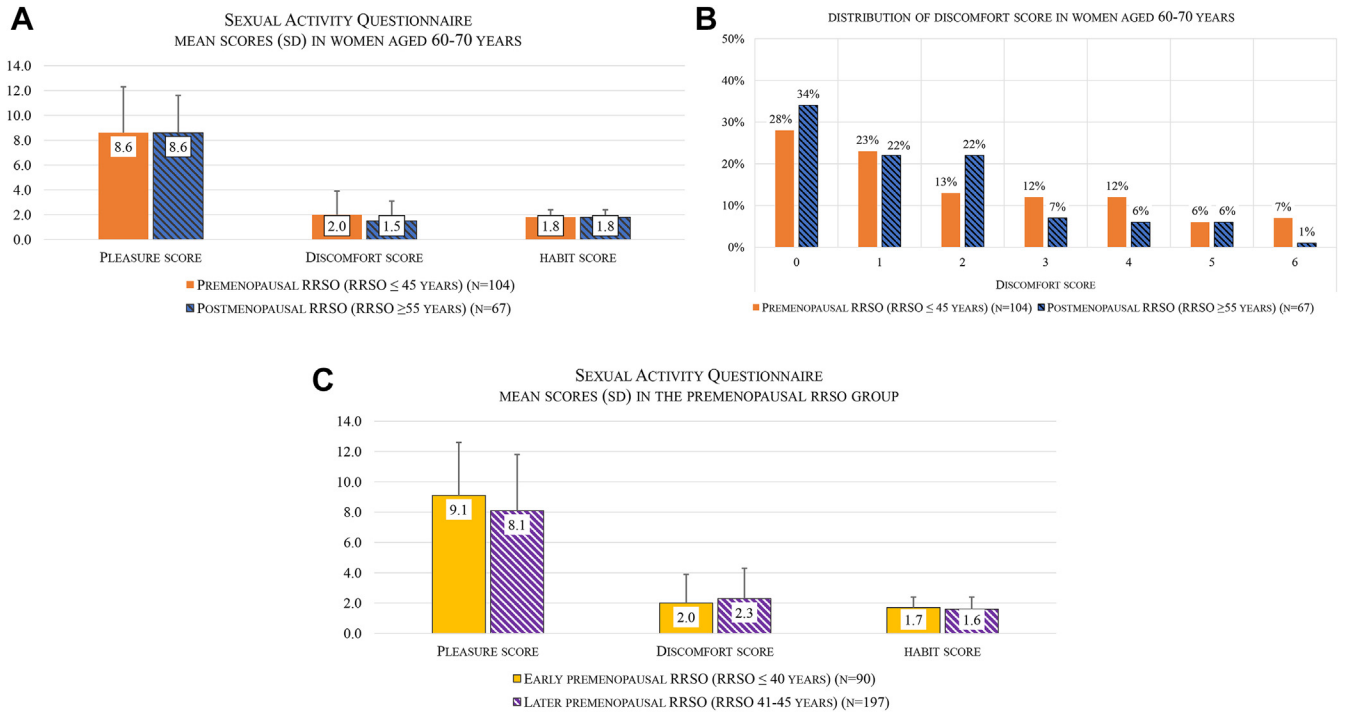
Vaginal dryness was assessed among women who were and were not sexually active. Women with a premenopausal RRSO reported more severe complaints of vaginal dryness, with 47.0% of women in the premenopausal group reporting substantial vaginal dryness compared with 31.1% of women in the postmenopausal RRSO group ($P<.001$) (Figure 4, B). Furthermore, after adjustment for confounders, a premenopausal RRSO was associated with substantial complaints of vaginal dryness (OR, 2.6; 95% CI, 1.4−4.7) (Table 3). Within the sexually active group, the results were similar; 46.1% of women with a premenopausal RRSO reported substantial complaints of vaginal dryness compared with 24.2% of women with a postmenopausal RRSO ($P<.01$) (Figure 4, A).

Subgroup analyses in the entire premenopausal risk-reducing salpingo-oophorectomy group

Timing of risk-reducing salpingo-oophorectomy (before age 41 years vs at ages 41 to 45 years)

Among women with an early premenopausal RRSO (before age 41, n=151), 56.0% were still sexually active at the time of questionnaire completion, compared with 60.9% in the late premenopausal RRSO group (RRSO at ages 41−45 years, n=348) ($P=.34$). Women with an early premenopausal RRSO did not differ from women with a late premenopausal RRSO concerning sexual pleasure or discomfort scores (Figure 3, C). Complaints about vaginal dryness were also similar (Figure 4, C); 42% of women in the early premenopausal RRSO group reported substantial vaginal dryness compared

FIGURE 3
Mean sexual activity subscale scores and standard deviation



A, Mean pleasure, discomfort, and habit scores in women aged 60 to 70 years comparing premenopausal RRSO with postmenopausal RRSO. Range pleasure score 0 to 18. Range discomfort score 0 to 6. Range habit score 0 to 3. **B,** Distribution of discomfort score in women aged 60 to 70 years comparing premenopausal RRSO with postmenopausal RRSO. **C,** Sexual activity questionnaire function subscales for women in the premenopausal RRSO group comparing early premenopausal RRSO with later premenopausal RRSO.

RRSO, risk-reducing salpingo-oophorectomy; *SD*, standard deviation.

Terra. Sexual functioning following premenopausal salpingo-oophorectomy. Am J Obstet Gynecol 2023.

with 49% of women in the late premenopausal RRSO group (P=.27).

Ever hormone replacement therapy use vs never hormone replacement therapy use in the premenopausal risk-reducing salpingo-oophorectomy group

Women with a premenopausal RRSO who never used HRT did not differ from ever HRT users regarding sexual pleasure scores (mean pleasure score of ever HRT users, 8.6 [SD, 3.7); mean pleasure score of never HRT users, 8.1 [SD, 3.4]; P=.32) or discomfort scores (mean discomfort score of HRT users, 2.0 [SD, 1.9]; mean discomfort score of never HRT users, 2.6 [SD, 1.9]; P=.06) (Supplementary Table 3). However, women who used HRT at the time of the study experienced less discomfort than never users (proportions with substantial discomfort of 15.0% and 38.8%, respectively; P=.04), and they also reported less vaginal dryness (current users, 20.8%; never users, 47.9%; P=.01). However, this comparison was based on only 26 current users.

Women with a premenopausal risk-reducing salpingo-oophorectomy with and without a history of breast cancer

Within the premenopausal RRSO group, we compared women with history of breast cancer (n=297) and women without history of breast cancer (n=220). The proportions of women who were sexually active and the mean pleasure and discomfort scores were similar between the groups (detailed results in Supplementary Table 3).

Comment

Principal findings

In this large cross-sectional study, we assessed long-term sexual functioning (>15 years) in women with a premenopausal RRSO (before the age of 46 years), compared with women with a postmenopausal RRSO (after the age of 54 years). After adjustment for age and breast cancer history, the proportion of sexually active women did not differ between the groups; at the age of 60 to 70 years, 48% of women in the premenopausal RRSO group were still sexually active compared with 45% of women in the postmenopausal RRSO group. Regarding sexual pleasure, the premenopausal and postmenopausal RRSO groups had similar results, indicating equal pleasure with sexual activity. However, after adjustment for confounders, such as age

TABLE 2
Associations between various patient characteristics and the presence of substantial discomfort during sexual intercourse in sexually active women

	Total sexually active women aged 60–70 y (n=171)				Total sexually active women in the premenopausal RRSO group (n=276)		
	Substantial discomfort,[a] n (%)	OR (95% CI) for substantial discomfort			Substantial discomfort,[a] n (%)	OR (95% CI) for substantial discomfort	
Timing of RRSO				Timing of RRSO			
Postmenopausal (RRSO at ≥54 y)	14 (20.9%)	1.00	(Ref)	Early premenopausal (RRSO at ≤40 y)	33 (37.5%)	1.00	(Ref)
Premenopausal (RRSO at ≤45 y)	37 (35.6%)	3.13	(1.04–9.36)	Later premenopausal (RRSO of 41–45 y)	78 (41.5%)	0.97	(0.56–1.69)
Age		1.15	(0.98–1.35)	Age		1.00	(0.92–1.08)
History of breast cancer				History of breast cancer			
No	21 (29.2%)	1.00		No	44 (35.8%)	1.00	(Ref)
Yes	30 (30.3%)	1.02		Yes	67 (43.2%)	1.32	(0.79–2.21)
BMI (continuous, per 1 kg/m^2 increase)		1.08	(1.00–1.16)	BMI (continuous, per 1 kg/m^2 increase)		NS	
BR23 body image (continuous, per 1 point more)		NS		BR23 body image (continuous, per 1 point more)		1.01	(1.00–1.03)
Constant		0.38*10^{-5}	(0.55*10^{-10} ;0.27)	Constant		0.64	(0.00 –85.23)

The discomfort score from the sexual activity questionnaire ranges from 0 to 6, with higher scores indicating more discomfort.

BMI, body mass index; *BR23*, body image score from the European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire; *CI*, confidence interval; *NA*, not applicable; *NS*, significance level of >.10, variable not in the multivariate model; *OR*, odds ratio; *Ref*, reference group; *RRSO*, risk-reducing salpingo-oophorectomy.

[a] Substantial discomfort was defined as a discomfort score of ≥3 (ie, 3, 4, 5, and 6). BR23 body image score ranges from 0 to 100.

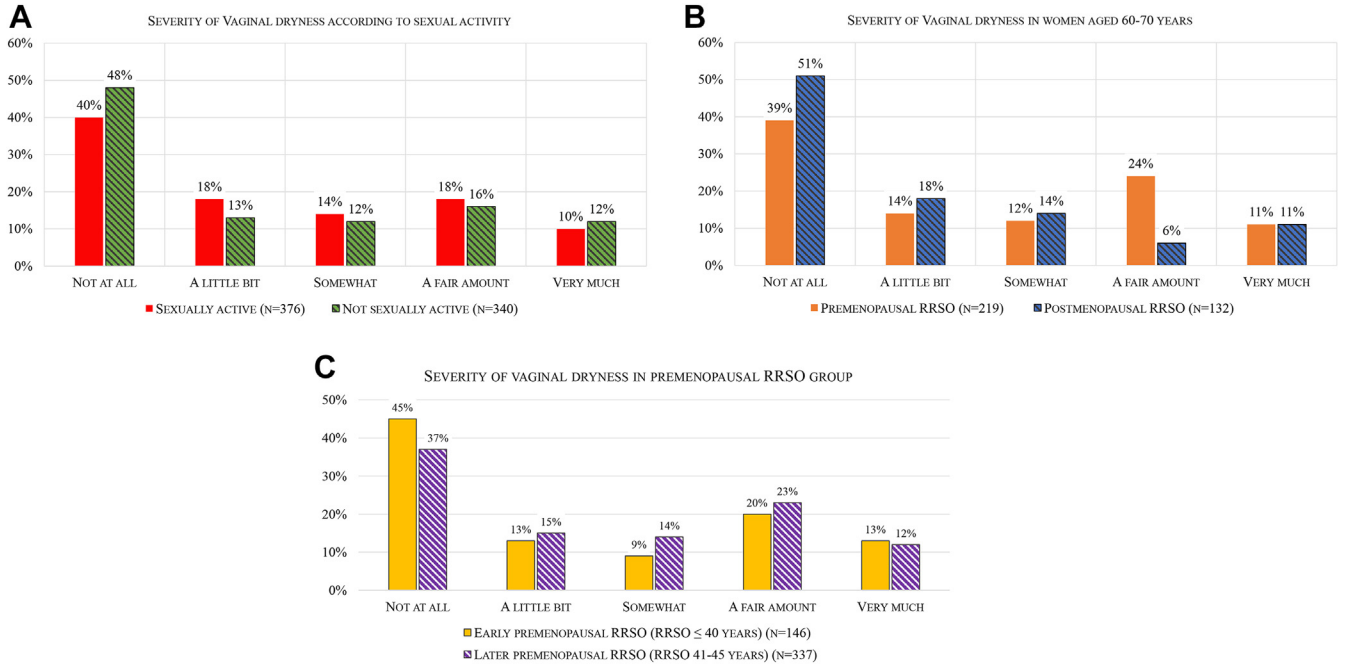
Terra. Sexual functioning following premenopausal salpingo-oophorectomy. Am J Obstet Gynecol 2023.

and breast cancer history, women with a premenopausal RRSO more often experienced substantial discomfort during sexual intercourse, because of more severe complaints of vaginal dryness. When comparing women with RRSO before the age of 41 years and RRSO at ages 41 to 45 years, there was no difference in mean discomfort scores or severity of vaginal dryness. Longer time since RRSO was not associated with the amount of discomfort. Noteworthy, more vaginal dryness was not associated with less pleasure with sexual intercourse. We have proposed several possible explanations. First, it is possible that women in our study experienced discomfort with sexual intercourse and, therefore, no longer engage in sex with penile penetration. However, they may be sexually active in other ways, from which they derive sexual pleasure without being bothered by discomfort from vaginal dryness. Second, it could be that women for whom sex is important are more proactive when it comes to coping mechanisms and exploring practical solutions, such as lubricants, to be able to be sexually active. Third, it is possible that we experienced a so-called "floor" effect in the scoring of the pleasure domain because most respondents did not consider sex a very important part of their life. Last, it is possible that the high scores in sexual satisfaction and the lower scores in arousal have attenuated the respondents' overall pleasure score. In line with previous literature, sexual pleasure, sexual discomfort, and/or the severity of vaginal dryness were not influenced by ever use of HRT.[14] However, women who used HRT at the time of the study experienced less discomfort and less vaginal dryness. As only 5.2% of women were current users, these results must be interpreted with caution.

Result in the context of what is known

To the best of our knowledge, the only study with normative data for the SAQ is a Norwegian study by Vistad et al.[22] Compared with this study, our subscale scores were lower, indicating less sexual pleasure, but also less discomfort. The frequency of sexual activity was comparable. In a study on sexual activity in a Dutch general population sample,[23] 52% of the 60- to 70-year-old participants were not sexually active, which is comparable with the 54% of participants in our

FIGURE 4
Severity of complaints of vaginal dryness



A, Overall study population: comparing women who were sexually active and women who were not sexually active. **B,** Women aged 60 to 70 years: comparing women with premenopausal RRSO with women with postmenopausal RRSO. **C,** Women with a premenopausal RRSO: comparing women with an RRSO before the age of 41 years and women with an RRSO at ages 41 to 45 years.

RRSO, risk-reducing salpingo-oophorectomy.

Terra. Sexual functioning following premenopausal salpingo-oophorectomy. Am J Obstet Gynecol 2023.

sample in the same age category. As they used the Female Sexual Function Index rather than the SAQ, other comparisons with our results were not possible.

Previous studies on sexual functioning after RRSO had short follow-ups (range, 3–6 years) and reported that, shortly after RRSO, women experienced more discomfort and less pleasure when engaging in sexual activity. Our study, with a mean follow-up of 18.3 years after RRSO, assessed the long-term effects of a premenopausal RRSO on sexual functioning and showed that, in the long run, pleasure with sexual activity is similar to that in women with a postmenopausal RRSO. However, women with premenopausal RRSO more often experienced substantial discomfort during sexual intercourse and had more severe complaints of vaginal dryness. Comparison of our study with other reports is difficult as there were many differences in study populations and methods of analysis. Age at RRSO varied widely across studies and the comparison groups used (eg, in some analyses, women with a premenopausal RRSO were combined with women with a postmenopausal RRSO). Moreover, in previous reports, the mean age in the study (40–57 years) was younger than in ours, rendering comparisons of sexual functioning between studies difficult. Furthermore, earlier studies did not always account for the confounding and potential modifying effects of a breast cancer history and HRT use. In our study, most women (77.8%) never used HRT; this was likely due to the high prevalence of previous breast cancer and conflicting reports regarding the safety of HRT in the period when our study population underwent RRSO.[24]

Clinical implications

Our study provided important information for clinicians counseling women who are considering risk-reducing surgery. It is crucial to give a complete overview of possible clinical and psychological sequelae and to set realistic expectations. Integrating our results with studies evaluating the short-term effects of RRSO, women can be informed that shortly after a premenopausal RRSO, they can expect less pleasure and more discomfort when engaging in sexual activity; in the long run, pleasure in sexual activity will not be different from that of women with RRSO after menopause. However, they can expect more discomfort with sexual intercourse and more vaginal dryness. Treating physicians should proactively discuss sexual functioning with their patients and provide advice,

TABLE 3
Association between various patient characteristics and the presence of substantial vaginal dryness for all women (sexually active and not sexually active)

	Vaginal dryness in women aged 60–70 y (n=351)				Vaginal dryness in women with a premenopausal RRSO (n=483)			
	Substantial vaginal dryness,[a] n (%)	OR (95% CI) for substantial vaginal dryness			Substantial vaginal dryness,[a] n (%)	OR (95% CI) for substantial vaginal dryness		
Timing of RRSO				Timing of RRSO		NA		
Postmenopausal (RRSO at ≥54 y)	41 (31.1%)	1.00	(Ref)	Early premenopausal (RRSO at ≤40 y)	61 (41.8%)	1.00	(Ref)	
Premenopausal (RRSO at ≤45 y)	103 (47.0%)	2.56	(1.40–4.68)	Later premenopausal (RRSO at 41–45 y)	165 (49.0%)	1.15	(0.75–1.77)	
Age		1.06	(0.97–1.16)	Age		1.02	(0.96–1.08)	
History of breast cancer				History of breast cancer				
No	57 (40.1%)	1.00	(Ref)	No	84 (42.6%)	1.00	(Ref)	
Yes	87 (41.6%)	1.04	(0.67–1.62)	Yes	142 (49.7%)	1.24	(0.83–1.85)	
Use of chronic medication[b]		NS		Use of chronic medication		NS		
No	63 (39.1%)			No	122 (44.9%)			
Yes	81 (42.6%)			Yes	104 (49.3%)			
BMI (continuous, per 1 kg/m^2 increase)		NS		BMI (continuous, per 1 kg/m^2 increase)		0.96	(0.92–1.00)	
Constant		0.01	(0.00–4.07)	Constant		0.81	(0.20–27.16)	

Vaginal dryness was assessed on a 5-point Likert scale with higher scores indicating more vaginal dryness (Functional Assessment of Cancer Therapy - Endocrine Symptoms).

BMI, body mass index; *CI*, confidence interval; *NA*, not applicable; *NS*, significance level of >.10; *OR*, odds ratio; *Ref*, reference group; *RRSO*, risk-reducing salpingo-oophorectomy.

[a] Substantial vaginal dryness was defined as having complaints of vaginal dryness as somewhat, quite a bit, or very much; [b] Chronic medication: any medication taken daily for cardiovascular risk factors, cardiovascular disease, or chronic disease.

Terra. Sexual functioning following premenopausal salpingo-oophorectomy. Am J Obstet Gynecol 2023.

including treatment options, in case of complaints.

Strengths and limitations

A limitation of our study, although inherent to the inclusion criterion regarding age at RRSO, was the difference in mean age at questionnaire completion between the premenopausal and the postmenopausal RRSO groups. During recruitment, it became clear that frequency-matching on current age was not possible, because, from 2007 onward, the national guideline for familial ovarian cancer strongly recommended RRSO for all women with *BRCA* PV, at the age of 35 to 40 years for *BRCA1* PV and at ages 41 to 45 for *BRCA2* PV carriers.[25] Consequently, most women (94.5%) with a postmenopausal RRSO were tested and underwent RRSO before 2007. To overcome this limitation, we performed analyses for women in the overlapping age range of 60 to 70 years at questionnaire completion. Another concern may be the difference in response rates between the premenopausal group (70.3%) and the postmenopausal group (48.0%). A likely explanation is that women in the postmenopausal RRSO group felt less inclined to participate as our research hypotheses were focused on early surgical menopause. However, we do not think this has affected our results, as it seems unlikely that current sexual activity would have affected study participation differently in women with premenopausal or postmenopausal RRSO. The HARMOny study invitation letter focused on the potential effects of premenopausal RRSO on cardiovascular disease and bone health. A last concern may be that, even though we defined sexual activity to include noncoital sex and masturbation in the instructions for completing the SAQ, we could not exclude the possibility that some women may have interpreted the questions as referring only to sexual intercourse. However, it is unlikely that such an interpretation would differ between the premenopausal and postmenopausal RRSO groups.

The strengths of our study included the large sample size, providing sufficient power to perform several subgroup

analyses. In addition, by excluding women with RRSO at ages 46 to 54 years, we were able to make a more distinct evaluation of the differences in sexual health between women who underwent RRSO before the onset of natural menopause and thereafter. Our participation rate was acceptable (59%), given the nature and focus of the study, and we employed validated questionnaires that are widely used. Moreover, all women in our study completed questions on vaginal dryness, not only women who were sexually active. More generally, our study assessed sexual functioning in a large group of women aged ≥60 years.

Conclusions

More than 15 years after premenopausal RRSO, women experienced more severe vaginal dryness and more discomfort with sexual intercourse than women with postmenopausal RRSO. However, this did not result in less pleasure with sexual activity. This knowledge can be integrated into presurgery counseling regarding expected sexual functioning after premenopausal RRSO. ■

References

1. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 2017;317:2402–16.
2. Nappi RE, Martini E, Cucinella L, et al. Addressing vulvovaginal atrophy (VVA)/genitourinary syndrome of menopause (GSM) for healthy aging in women. Front Endocrinol (Lausanne) 2019;10:561.
3. Mac Bride MB, Rhodes DJ, Shuster LT. Vulvovaginal atrophy. Mayo Clin Proc 2010;85:87–94.
4. Robinson D, Cardozo LD. The role of estrogens in female lower urinary tract dysfunction. Urology 2003;62(Suppl1):45–51.
5. Sturdee DW, Panay N; International Menopause Society Writing Group. Recommendations for the management of postmenopausal vaginal atrophy. Climacteric 2010;13:509–22.
6. Waetjen LE, Crawford SL, Chang PY, et al. Factors associated with developing vaginal dryness symptoms in women transitioning through menopause: a longitudinal study. Menopause 2018;25:1094–104.
7. Stuursma A, van Driel CMG, Wessels NJ, de Bock GH, Mourits MJE. Severity and duration of menopausal symptoms after risk-reducing salpingo-oophorectomy. Maturitas 2018;111:69–76.
8. Faubion SS, Kuhle CL, Shuster LT, Rocca WA. Long-term health consequences of premature or early menopause and considerations for management. Climacteric 2015;18:483–91.
9. Madalinska JB, van Beurden M, Bleiker EM, et al. The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women after prophylactic salpingo-oophorectomy. J Clin Oncol 2006;24:3576–82.
10. Kershaw V, Hickey I, Wyld L, Jha S. The impact of risk reducing bilateral salpingo-oophorectomy on sexual function in BRCA1/2 mutation carriers and women with Lynch syndrome: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 2021;265:7–17.
11. Tucker PE, Bulsara MK, Salfinger SG, Tan JJ, Green H, Cohen PA. Prevalence of sexual dysfunction after risk-reducing salpingo-oophorectomy. Gynecol Oncol 2016;140:95–100.
12. Robson M, Hensley M, Barakat R, et al. Quality of life in women at risk for ovarian cancer who have undergone risk-reducing oophorectomy. Gynecol Oncol 2003;89:281–7.
13. Finch A, Metcalfe KA, Chiang JK, et al. The impact of prophylactic salpingo-oophorectomy on menopausal symptoms and sexual function in women who carry a BRCA mutation. Gynecol Oncol 2011;121:163–8.
14. Hall E, Finch A, Jacobson M, et al. Effects of bilateral salpingo-oophorectomy on menopausal symptoms and sexual functioning among women with a BRCA1 or BRCA2 mutation. Gynecol Oncol 2019;152:145–50.
15. Mai PL, Huang HQ, Wenzel LB, et al. 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. Gynecol Oncol 2020;156:131–9.
16. Terra L, Hooning MJ, Heemskerk-Gerritsen BAM, et al. Long-term morbidity and health after early menopause due to oophorectomy in women at increased risk of ovarian cancer: protocol for a nationwide cross-sectional study with prospective follow-up (HARMOny study). JMIR Res Protoc 2021;10:e24414.
17. Schrijver LH, Olsson H, Phillips KA, et al. Oral contraceptive use and breast cancer risk: retrospective and prospective analyses from a BRCA1 and BRCA2 mutation carrier cohort study. JNCI Cancer Spectr 2018;2:pky023.
18. Wevers MR, Schmidt MK, Engelhardt EG, et al. Timing of risk reducing mastectomy in breast cancer patients carrying a BRCA1/2 mutation: retrospective data from the Dutch HEBON study. Fam Cancer 2015;14:355–63.
19. Sprangers MA, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol 1996;14:2756–68.
20. Thirlaway K, Fallowfield L, Cuzick J. The Sexual Activity Questionnaire: a measure of women's sexual functioning. Qual Life Res 1996;5:81–90.
21. Madalinska JB, Hollenstein J, Bleiker E, et al. Quality-of-life effects of prophylactic salpingo-oophorectomy versus gynecologic screening among women at increased risk of hereditary ovarian cancer. J Clin Oncol 2005;23:6890–8.
22. Vistad I, Fosså SD, Kristensen GB, Mykletun A, Dahl AA. The sexual activity questionnaire: pychometric properties and normative data in a Norwegian population sample. J Womens Health (Larchmt) 2007;16:139–48.
23. Lammerink EAG, de Bock GH, Pascal A, et al. A survey of female sexual functioning in the General Dutch population. J Sex Med 2017;14:937–49.
24. Ameye L, Antoine C, Paesmans M, de Azambuja E, Rozenberg S. Menopausal hormone therapy use in 17 European countries during the last decade. Maturitas 2014;79:287–91.
25. Hermsen BB, Olivier RI, Verheijen RH, et al. No efficacy of annual gynaecological screening in BRCA1/2 mutation carriers; an observational follow-up study. Br J Cancer 2007;96:1335–42.

Author and article information

From the Division of Psychosocial Research and Epidemiology, The Netherlands Ca Erancer Institute, Amsterdam, The Netherlands (Drs Terra, Beekman, Engelhardt, Aaronson, and van Leeuwen); Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands (Drs Heemskerk-Gerritsen and Hooning); Department of Gynecologic Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands (Dr van Beurden); Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands (Dr Roeters van Lennep); Department of Gynecologic Oncology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands (Dr van Doorn); Department of Gynecology, Radboud University Medical Center, Nijmegen, The Netherlands (Dr de Hullu); Department of Gynecologic Oncology, University Medical Center Utrecht, Utrecht, The Netherlands (Dr Van Dorst); Department of Gynecologic Oncology, Amsterdam University Medical Center, Amsterdam, The Netherlands (Dr Mom); Department of Obstetrics and Gynecology, Maastricht University Medical Centre, Maastricht, The Netherlands (Dr Slangen); GROW-School for Oncology and Developmental Biology, Maastricht, The Netherlands (Dr Slangen); Department of Obstetrics and Gynecology, Leiden University Medical Center, Leiden, The Netherlands (Dr Gaarenstroom); Family Cancer Clinic, The Netherlands Cancer Institute, Amsterdam, The Netherlands (Dr van der Kolk); Department of Clinical Genetics, Erasmus MC Cancer Institute, Rotterdam, The Netherlands (Dr Collée); Department of Clinical Genetics, Radboud University Medical Center, Nijmegen, The Netherlands (Dr Wevers); Division of Laboratories, Pharmacy, and Biomedical Genetics, Department of Genetics, University Medical Centre Utrecht, Utrecht, The Netherlands (Dr Ausems); Department of Human Genetics, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands (Drs Van Engelen and van de Beek); Department of Genetics,

University of Groningen, University Medical Center Groningen, Groningen, The Netherlands (Dr Berger); Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands (Dr van Asperen); Department of Clinical Genetics, Maastricht University Medical Center, Maastricht, The Netherlands (Dr Gomez Garcia); Department of Cardiology, Radboud University Medical Center, Nijmegen, The Netherlands (Dr Maas); and Department of Gynecologic Oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands (Dr Mourits).

Received July 8, 2022; revised Oct. 21, 2022; accepted Nov. 10, 2022.

The authors report no conflict of interest.

The Dutch Cancer Society (KWF) and the Maarten van der Weijden Foundation have provided funding for this project (registered under grant number 10164). The funding body had no role in the design of the study; collection, analysis, and interpretation of data; or writing of the manuscript.

This study was registered on ClinicalTrials.gov on February 11, 2019 (file number: NCT03835793; https://clinicaltrials.gov/ct2/show/NCT03835793).

With publication, deidentified data collected for the study, including participant data, will be made available to others on reasonable request. Data can be requested with a proposal by sending an e-mail to the corresponding author. Study protocol and statistical analysis plan are available on ClinicalTrials.gov (file number NCT03835793).

This study will be conducted according to the standards of Good Clinical Practice, in agreement with the principles of the Declaration of Helsinki and with the Dutch law as stated in the Medical Research Involving Human Subjects Act (WMO). The study has been approved in writing by the institutional review board of the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital to be conducted in all 9 University Medical Centers and the Antoni van Leeuwenhoek and has been registered at "CCMO Toetsingonline" from the Dutch Central Committee on Research involving Human Subjects (file number: NL63554.031.17) and on ClinicalTrials.gov (M18HAR). The results will be disseminated through peer-reviewed publications and will be incorporated in follow-up guidelines.

Corresponding author: Flora E. van Leeuwen, PhD. f.v.leeuwen@nki.nl

Supplementary material

Reasons for sexual inactivity

Among women who were not sexually active (n=355), not having a partner and arousal problems were the reasons reported most frequently in the premenopausal RRSO group (Supplementary Table 2). An arousal problem was the reason for sexual inactivity for 31.4% of women with a premenopausal RRSO and, for 23.4 % of women with a postmenopausal RRSO (*p-value* .04). Women in the premenopausal RRSO group reported more often fatigue as a reason for sexual inactivity (13.3% in the premenopausal group versus 4.1% in the postmenopausal RRSO group, *p-value* <.01). Women in the postmenopausal RRSO group more often reported that their partner had a physical problem interfering with sexual activity (premenopausal RRSO group 15.7%, postmenopausal RRSO group 27.6%, *p*-value .02).

Sexual Activity Questionnaire - Habit score

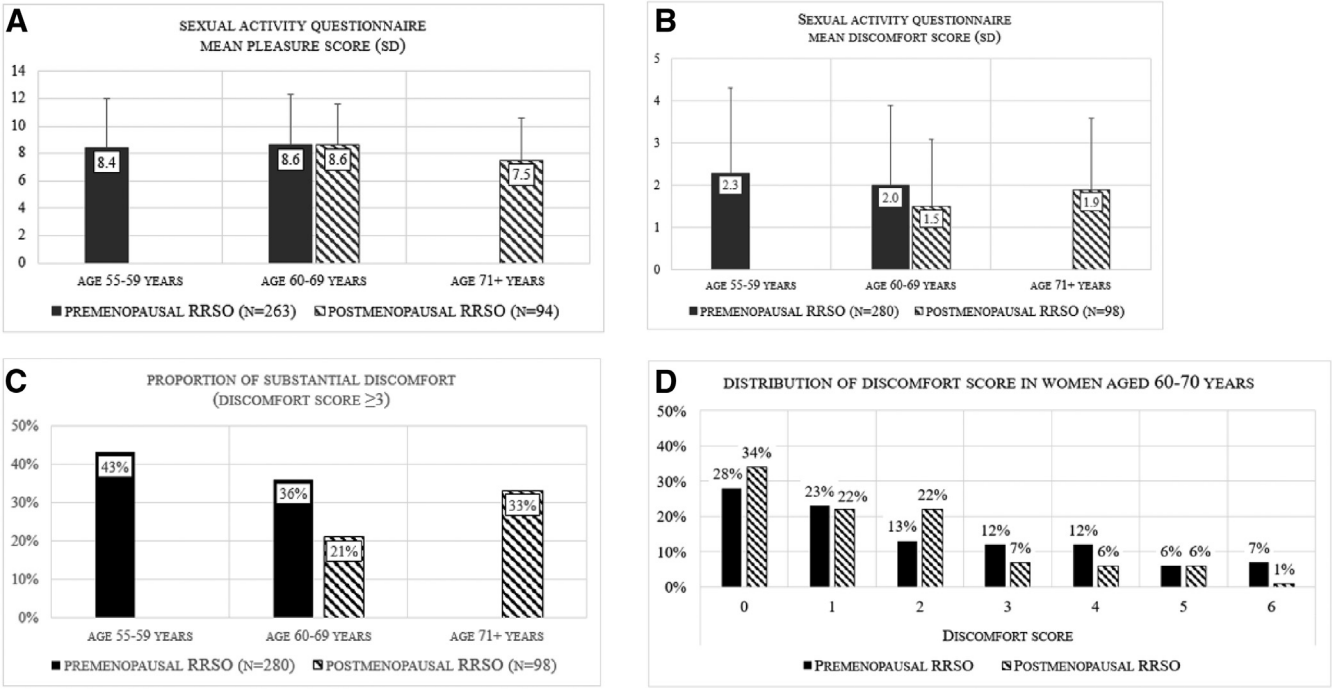
The SAQ-habit score was comparable between the premenopausal RRSO and the postmenopausal RRSO groups (1.6 versus 1.8, *p-value* .16). This was also true for women aged 60-70 years; 1.8 (SD 0.6) in the premenopausal RRSO group and 1.8 (SD 0.7) in the postmenopausal RRSO group (supplementary Figure 1).

References

1. Thirlaway K, Fallowfield L, Cuzick J. The Sexual Activity Questionnaire: a measure of women's sexual functioning. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation Feb 1996;5(1):81–90.

2. Sprangers MA, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology Oct 1996;14(10): 2756–68. https://doi.org/10.1200/JCO.1996.14.10.2756.

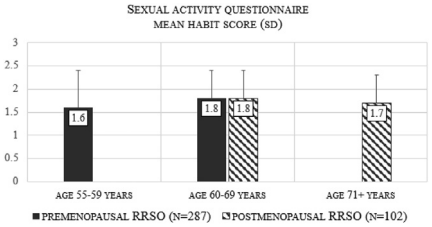
SUPPLEMENTARY FIGURE 1
Mean sexual activity subscale scores and standard deviation by age category at completion of questionnaire



(**a**) Mean pleasure scores. Range pleasure score 0 − 18. Age 55-59 years: Premenopausal RRSO n=162, postmenopausal RRSO n= 0; Age 60-70 years: premenopausal RRSO n=99, postmenopausal RRSO n=65; Age 71+ years: premenopausal RRSO n=0, postmenopausal RRSO n= 28. (**b**) Mean discomfort scores. Range discomfort score 0 − 6. Age 55-59 years: Premenopausal RRSO n=173, postmenopausal RRSO n= 0; Age 60-70 years: premenopausal RRSO n=104, postmenopausal RRSO n=67; Age 71+ years: premenopausal RRSO n=1, postmenopausal RRSO n= 30. (**c**) Proportion of women with a substantial discomfort score (discomfort score ≥ 3). **(d)** The distribution of women aged 60-70 years per discomfort score.

Terra. Sexual functioning following premenopausal salpingo-oophorectomy. Am J Obstet Gynecol 2023.

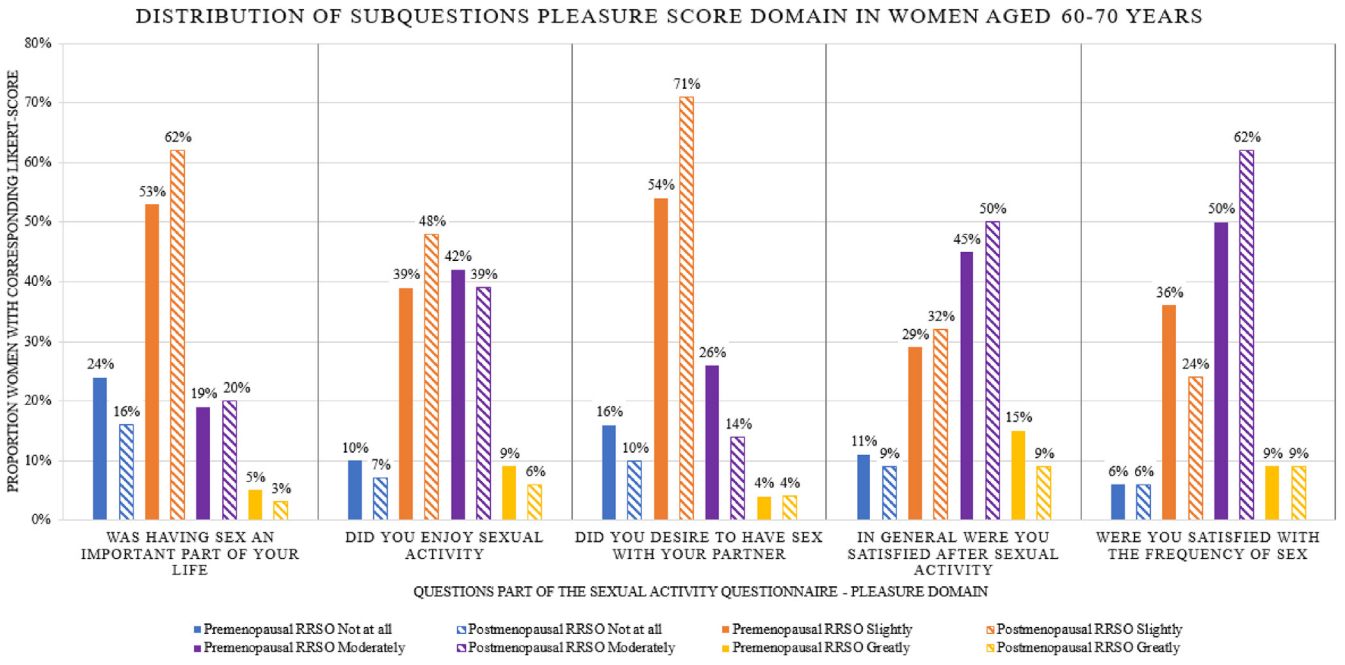
SUPPLEMENTAL FIGURE 2
Mean habit score and the corresponding standard deviation, in the premenopausal and postmenopausal RRSO groups per age group



Range habit score 0 − 3. Age 55-59 years: Premenopausal RRSO n=178, postmenopausal RRSO n= 0; Age 60-70 years: premenopausal RRSO n=108, postmenopausal RRSO n=70; Age 71+ years: premenopausal RRSO n=1, postmenopausal RRSO n= 32.

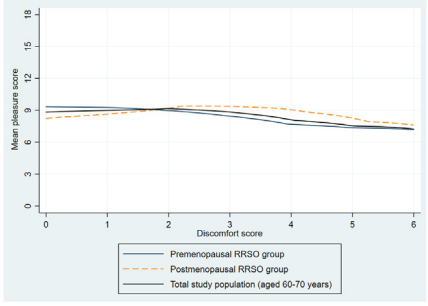
Terra. Sexual functioning following premenopausal salpingo-oophorectomy. Am J Obstet Gynecol 2023.

SUPPLEMENTARY FIGURE 3
Distribution of answers given to the questions that cover the pleasure scale



Terra. Sexual functioning following premenopausal salpingo-oophorectomy. Am J Obstet Gynecol 2023.

SUPPLEMENTARY FIGURE 4
Mean pleasure score in relation to the discomfort score in women aged 60-70 years at study comparing women with a premenopausal RRSO with women with a postmenopausal RRSO



Terra. Sexual functioning following premenopausal salpingo-oophorectomy. Am J Obstet Gynecol 2023.

SUPPLEMENTARY TABLE 1
Sexual activity questionnaire

Questionnaire	Questions	Scoring system
Sexual activity questionnaire (SAQ)[1]	Sexual active / not I am not sexually active at the moment because*: ■ I do not have a partner ■ I am too tired ■ My partner is too tired ■ I am not interested in sex ■ My partner is not interested in sex ■ I have a physical problem which makes sexual relations difficult or uncomfortable ■ My partner has a physical problem which makes sexual relations difficult or uncomfortable *multiple reasons per person possible Domains: • Pleasure 1. Was having sex an important part of your life 2. Did you enjoy sexual activity 3. Did you desire to have sex with your partner? 4. In general were you satisfied after sexual activity 5. How often did you engage in sexual activity 6. Were you satisfied with the frequency of sex • Discomfort 1. Did you notice dryness of your vagina this month during sexual intercourse 2. Did you feel pain or discomfort with sexual intercourse this month? • Habit 1. How did the frequency of sexual behavior compare with what is usual for you?	9 items with a 4-point Likert scale. 0 = not at all, 1 = slightly, 2 = moderately, 3 = greatly. Domain scores were obtained by adding together the weighted loadings for each question that contributed to each factor. Subscale scores: Pleasure 0-18; higher scores indicate higher level of pleasure. Discomfort 0-6; higher scores indicate higher levels of discomfort. Habit 0-3; single item. 0 = less sexual activity than usual to 3=much more sexual activity than usual.
European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23)[2] body image questions	Did you feel yourself physically less attractive as a consequence from your illness or treatment? Did you feel less feminine as a consequence from your illness or treatment? Did you found it difficult to see yourself naked? Were you unhappy with your body?	Assessed on a 4-point Likert scale. 1 = not at all, 2 = slightly, 3 = moderately, 4 = greatly The scale is linearly transformed to a score range 0 − 100 with higher scores represents higher levels of functioning.
Functional Assessment of Cancer Therapy - Endocrine Symptoms (FACT-ES)[2]	I have vaginal discharge I have vaginal itching/irritation I have vaginal bleeding/spotting I have vaginal dryness I have pain or discomfort with intercourse	Assessed on a 5-point Likert scale. 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much

Terra. Sexual functioning following premenopausal salpingo-oophorectomy. Am J Obstet Gynecol 2023.

SUPPLEMENTARY TABLE 2
Additional characteristics of all study participants

	Entire study population		Women aged 60-70 years	
	Premenopausal RRSO (n=499)	Postmenopausal RRSO (n=256)	Premenopausal RRSO (n=226)	Postmenopausal RRSO (n=142)
Psychological interventions taken for menopausal complaints (yes)	45 (9.0%)	15 (5.9%)	12 (5.3%)	7 (4.9%)
Dietary intervention for menopausal complaints (yes)	43 (8.6%)	9 (3.5%)	14 (6.2%)	6 (4.2%)
Physical exercise for menopausal complaints (yes)	27 (5.4%)	12 (4.7%)	13 (5.8%)	6 (4.2%)
BMI (mean, SD)	26.5 (5.0)	25.8 (4.5)	26.6 (5.2)	26.2 (5.0)
Smoking status at study questionnaire				
Non-smoker	250 (50.1%)	112 (43.8%)*	94 (41.6%)	64 (45.1%)
Former smoker	211 (42.3%)	134 (52.3%)*	106 (46.9%)	64 (45.1%)
Current smoker	36 (7.2%)	9 (3.5%)*	18 (8.0%)	7 (4.9%)
Pack-years smoked (mean, SD)	14.5 (11.4)	17.0 (15.4)	23.9 (14.4)	23.8 (15.1)
Educational level				
Primary school/lower level high school	138 (27.6%)	109 (42.6%)*	66 (29.2%)	51 (35.9%)
Middle level high school	165 (33.1%)	45 (17.6%)*	68 (30.1%)	34 (23.9%)
Advanced vocational/university	158 (31.7%)	81 (31.6%)*	77 (34.1%)	44 (31.0%)
Employment status at study questionnaire				
Full-time job/part-time job	282 (56.5%)	29 (11.3%)*	109 (48.2%)	25 (17.6%)*
Retired	35 (7.0%)	159 (62.1%)*	29 (12.8%)	71 (50.0%)*
Housewife/voluntary work	42 (8.4%)	23 (9.0%)*	25 (11.1%)	14 (9.9%)*
Completely/partially incapacitated for work	51 (10.2%)	7 (2.7%)*	21 (9.3%)	7 (4.9%)*
(temporary) Unemployed	44 (8.8%)	11 (4.3%)*	23 (10.2%)	10 (7.0%)*

Abbreviations: RRSO: risk-reducing salpingo-oophorectomy; SD: standard deviation; BMI: body mass index; HRT: hormone replacement therapy in sexually active women.

* *P*-value <.05. Groups compared using independent samples *t*-test, Chi-squared test or Fishers exact test.

Terra. Sexual functioning following premenopausal salpingo-oophorectomy. Am J Obstet Gynecol 2023.

SUPPLEMENTARY TABLE 3

Reasons for sexual inactivity in women who are not sexually active (multiple reasons per person possible)

	Premenopausal RRSO (n=210)	Postmenopausal RRSO (n=145)	*p*-value
No partner	60 (28.6%)	47 (32.4%)	.75
Arousal problem	66 (31.4%)	34 (23.4%)	.04
Fatigue	28 (13.3%)	6 (4.1%)	<.01
Physical problem	48 (22.9%)	29 (20.0%)	.32
Partner fatigue	12 (5.7%)	6 (4.1%)	.41
Partner physical problem	33 (15.7%)	40 (27.6%)	.02
No reason given	39 (18.6%)	30 (20.7%)	.83

Terra. Sexual functioning following premenopausal salpingo-oophorectomy. Am J Obstet Gynecol 2023.

SUPPLEMENTARY TABLE 4
SAQ function scores per analysis performed

Total study population

Number			Sexually active (YES)	*p*-value	SAQ pleasure score (mean (SD))	*p*-value	SAQ discomfort score (mean (SD))	*p*-value	SAQ habit score (mean (SD))	*p*-value
1	Premenopausal RRSO (RRSO ≤ 45 years)	499	57.9%	<.001	8.5 (3.6)	.75	2.2 (2.0)	.01	1.7 (.7)	.21
	Postmenopausal RRSO (RRSO ≥ 54 years)	256	39.8%		8.3 (3.1)		1.6 (1.6)		1.8 (.6)	
2	Premenopausal RRSO & ages 60-70 years at questionnaire completion	226	47.4%	.09	8.6 (3.7)	.99	2.0 (1.9)	.09	1.8 (.6)	.78
	Postmenopausal RRSO & ages 60-70 years at questionnaire completion	142	48.9%		8.6 (3.0)		1.5 (1.6)		1.8 (.6)	
3	Premenopausal RRSO & history of breast cancer (YES)	293	54.6%	<.01	8.3 (3.6)	.68	2.3 (1.9)	.02	1.7 (.7)	.17
	Postmenopausal RRSO & history of breast cancer (YES)	166	41.0%		8.1 (3.1)		1.7 (1.6)		1.8 (.5)	
4	Premenopausal RRSO & history of breast cancer (NO)	204	62.3%	<.001	8.7 (3.7)	.98	2.0 (2.0)	.25	1.6 (.7)	.99
	Postmenopausal RRSO & history of breast cancer (NO)	89	37.1%		8.7 (3.1)		1.6 (1.7)		1.6 (.8)	

Premenopausal RRSO (RRSO ≤ 45 years)

Number			Sexually active (YES)	*p*-value	SAQ pleasure score (mean (SD))	*p*-value	SAQ discomfort score (mean (SD))	*p*-value	SAQ habit score (mean (SD))	*p*-value
5	Early premenopausal RRSO (RRSO ≤ 40 years)	151	59.6%	.55	9.1 (3.5)	.05	2.0 (1.9)	.41	1.7 (.7)	.90
	Later premenopausal RRSO (RRSO 41-45 years)	348	56.7%		8.1 (3.7)		2.3 (2.0)		1.6 (.8)	
6	Current HRT-users	26	72.9%	.09	9.6 (4.5)	.16	1.1 (1.5)	.01	1.4 (.9)	.01
	Former HRT-users	101	59.4%		8.1 (3.3)		2.5 (2.1)		1.5 (.8)	
	Never HRT-users	332	55.1%		8.5 (3.6)		2.2 (1.9)		1.7 (.7)	
7	History of breast cancer (YES)	293	54.6%	.09	8.3 (3.6)	.42	2.3 (1.9)	.20	1.7 (.7)	.20
	History of breast cancer (NO)	204	62.3%		8.7 (3.7)		2.0 (2.0)		1.6 (.7)	

Premenopausal RRSO group compared with the postmenopausal RRSO group in: (1) entire study population, (2) women aged 60-70 years at questionnaire completion, (3) women with a history of breast cancer, and (4) women without a history of breast cancer. Within the premenopausal RRSO group we compared (5) early premenopausal RRSO with later premenopausal RRSO, (6) Current or former HRT-users with never HRT users and (7) women with and without a history of breast cancer.

Terra. Sexual functioning following premenopausal salpingo-oophorectomy. Am J Obstet Gynecol 2023.

SUPPLEMENTARY TABLE 5

Association between various patient characteristics and the presence of substantial discomfort during sexual intercourse for sexually active women

	All sexually active women (n= 378)		
	Substantial discomfort* (n (%))	OR (95% CI) for substantial discomfort	
Timing of RRSO			
Postmenopausal (RRSO ≥ 54 years)	24 (24.5%)	1.00	(REF)
Premenopausal (RRSO ≤ 45 years)	111 (39.6%)	3.41	(1.29;9.03)
Age			
55-59 years		1.00	(REF)
60-64 years		.60	(.34;1.07)
65-70 years		1.34	(.56;3.25)
71+ years		1.98	(.55;7.12)
History of breast cancer			
No	51 (32.7%)	1.00	(REF)
Yes	84 (38.4%)	1.28	(0.81;2.04)
BMI (continuous, per 1 kg/m^2 increase)		NS	
BR23-body image (continuous, per 1 point more)		1.01	(1.00;1.03)
Constant		0.17	(0.06;0.49)

The discomfort score from the sexual activity questionnaire ranges from 0-6, with higher scores indicating more discomfort.

Abbreviations: OR: odds ratio; CI: confidence interval; RRSO: risk-reducing salpingo-oophorectomy; BMI: body mass index; BR23-body image: body image score from the European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire, score range 0-100; NA: not applicable; NS: significance level >.10, variable not in multivariate model.

* Substantial discomfort was defined as a discomfort score of 3 or higher (i.e. 3, 4, 5, 6).

Terra. Sexual functioning following premenopausal salpingo-oophorectomy. Am J Obstet Gynecol 2023.

SUPPLEMENTARY TABLE 6

Association between various patient characteristics and the presence of substantial vaginal dryness for all women (sexually active and not sexually active)

	Vaginal dryness all women (n=716)		
	Substantial vaginal dryness* (n (%))	OR (95% CI) for substantial vaginal dryness	
Timing of RRSO			
Postmenopausal (RRSO ≥ 54 years)	64 (27.5%)	1.00	(REF)
Premenopausal (RRSO ≤ 45 years)	226 (46.8%)	2.28	(1.25;4.16)
Age			
55-59 years		1.00	(REF)
60-64 years		.87	(.57;1.33)
65-70 years		1.25	(.68;2.29)
71+ years		.72	(.32;1.61)
History of breast cancer			
No	105 (37.8%)	1.00	(REF)
Yes	185 (42.2%)	1.25	(0.89;1.77)
Use of chronic medication†			
No	145 (38.8%)	1.00	(REF)
Yes	145 (42.4%)	1.44	(1.01;2.05)
BMI (continuous, per 1 kg/m^2 increase)		0.97	(0.93;1.00)
Constant		0.65	(0.21;2.00)

Vaginal dryness was assessed on a 5-point likert scale with higher scores indicating more vaginal dryness (FACT-ES).

Abbreviations: OR: odds ratio; CI: confidence interval; RRSO: risk-reducing salpingo-oophorectomy; BMI: body mass index; NA: not applicable; NS: significance level >.10.

* Substantial vaginal dryness was defined as having somewhat – quite a bit or very much complaints regarding vaginal dryness; † Chronic medication: any medication taken daily for cardiovascular risk factors, cardiovascular disease or chronic disease.

Terra. Sexual functioning following premenopausal salpingo-oophorectomy. Am J Obstet Gynecol 2023.