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

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**Trial submission**

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iii. Clinical trial identification number: NCT 03835793

iv. URL of registration site: https://clinicaltrials.gov/ct2/home

v. Data sharing information: With publication, de-identified data collected for the study, including participant data, will be made available to others upon 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.

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AJOG at a glance:

A. Why was this study conducted

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

B. What are the 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

C. What does this study add to what is already known

• Information on long-term sexual functioning after premenopausal risk-reducing salpingo-oophorectomy
Abstract

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 one to three years after a premenopausal oophorectomy. However, the long-term effects of a premenopausal oophorectomy on sexual functioning are unknown.

Objective

Our aim was to study long-term sexual functioning in women at increased familial risk of breast/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).

We performed subgroup analyses 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, we invited 817 women with a high familial risk of breast/ovarian cancer from an ongoing cohort study to participate in our study. Due to a large difference in age at study between the premenopausal and postmenopausal salpingo-oophorectomy groups, we restricted the comparison of sexual functioning between the groups to 368 women who were 60-70 years old at completion of the questionnaire (premenopausal group, n=226, postmenopausal group, n=142). In 496 women with a premenopausal risk-reducing salpingo-oophorectomy we compared sexual functioning between women in the early premenopausal group (n=151) and 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/no) and body image.

Results

Mean time since risk-reducing salpingo-oophorectomy was 20.6 years in the premenopausal group and 10.6 years in the postmenopausal group (p-value < .001). In the premenopausal group, mean age at questionnaire completion was 62.7 years, versus 67.0 years in the postmenopausal group (p < .001). In the premenopausal group, 47.4% was still sexually active, compared to 48.9% of the postmenopausal group (p-value: .80). Current sexual pleasure scores were the same for women in the premenopausal group and the postmenopausal group (mean pleasure score 8.6, p-value .99). However, women in the premenopausal group more often reported substantial discomfort than women in the postmenopausal group (35.6% compared with 20.9%, p-value .04). After adjusting for confounders, premenopausal risk-reducing salpingo-oophorectomy was associated with substantially more discomfort during sexual intercourse, compared to postmenopausal risk-reducing salpingo-oophorectomy (odds ratio 3.1, 95% confidence interval 1.04; 9.4). Moreover, following 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 age 41 reported similar pleasure and discomfort scores as women with a risk-reducing salpingo-oophorectomy between ages 41 and 45.

Conclusion

More than 15 years after premenopausal risk-reducing salpingo-oophorectomy, the proportion of sexually active women was comparable to that among 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.

Keywords

BRCA pathogenic variants, BRCA1, BRCA2, ovariectomy, sexual pleasure, sexual discomfort, surgical menopause, vaginal dryness
Introduction

Risk-reducing salpingo-oophorectomy (RRSO) is performed to prevent ovarian/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 35-40 years for BRCA1 PV carriers, and at ages 40-45 years for BRCA2 PV carriers.\(^1\) RRSO induces an immediate menopause which may result in short-term and long-term morbidity such as decreased psychosexual functioning.

Reduced circulating estrogen levels due to menopause result in vulvovaginal atrophy, which may predispose to micro-traumata 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 due to the risk of breast cancer.

Several studies have examined the effect of RRSO on sexual functioning.\(^10\) Most showed that, shortly after RRSO, women experienced more discomfort and less pleasure with sexual activity.\(^11-14\) However, this difference was not observed six years after RRSO.\(^15\) It is possible that women developed coping mechanisms or explored practical solutions, in the years following 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, i.e. breast cancer history and HRT use, was done inconsistently. Also, there are no long-term data on the impact of duration of menopause on sexual functioning.

The aim of this study was to investigate the impact of a premenopausal RRSO on sexual functioning after at least 10 years. To overcome 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/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

Participants were Dutch women participating in the HARMOny study16 (ClinicalTrials.gov NCT03835793): a multicenter cross-sectional study, nested in a cohort of women at high familial risk of breast/ovarian cancer.17,18 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. Eligibility criteria included a high familial risk of breast/ovarian cancer, current age of ≥55 years and having undergone RRSO either before age 45 or after age 54. 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 use of HRT (never, former, current use) and alternatives for HRT (e.g. herbal supplements, cognitive behavioral therapy, exercise). The questionnaire extensively addressed menopausal symptoms, including vaginal dryness, and body image (Supplementary Table 1).19
We assessed sexual functioning using the Sexual Activity Questionnaire (SAQ) (Supplementary Table 1).\textsuperscript{20} The SAQ is a validated questionnaire\textsuperscript{21,22} and consists of three 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 on non-coital intercourse and masturbation. The questionnaire employs a 4-point Likert scale (‘very much’, ‘somewhat’, ‘a little’, ‘not at all’). A composite score was calculated for ‘pleasure’ (range 0-18), ‘discomfort’ (range 0-6) and ‘habit’ (i.e. frequency of habitual sexual activity, range 0-3).\textsuperscript{20,22}

**Statistical analyses**

Differences in characteristics between the premenopausal and the postmenopausal RRSO groups were evaluated using the $\chi^2$ test or Fisher’s exact test for categorical data, and independent samples t-test for continuous data.

The association between 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 (95%CI). We created dichotomous variables for the discomfort score and the severity of vaginal dryness, comparing no/some discomfort (discomfort score $\leq$2) with substantial discomfort (discomfort score $\geq$3), and no/somewhat vaginal dryness (score $\leq$3) with substantial vaginal dryness (score $\geq$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, BMI, hysterectomy (yes/no), preventive mastectomy (yes/no), chronic medication use (yes/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. Due to 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’.

We also 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) was used. P-values <.05 were considered statistically significant.

**Results**

**Participation**

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

[INSERT FIGURE 1 AROUND HERE]

**Participant characteristics**

In the complete study population, mean age at questionnaire completion was 60.0 years in the premenopausal group, compared to 70.2 years in the postmenopausal group (p-value <.001)
Compared to the postmenopausal RRSO group, women in the premenopausal group more often had a partner (83.7% versus 72.9%, p-value .001) and were more often sexually active (57.6% versus 39.3%, p-value <.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 60-70 years old at completion of the questionnaire (premenopausal group, n=226, postmenopausal group, n=142). Within all 496 women with a premenopausal risk-reducing salpingo-oophorectomy we compared sexual functioning between women in the early premenopausal group (n=151) and the later premenopausal group (n=345). Results from analyses of the complete study population are provided in supplementary tables S1.

Among women aged 60-70 years at study, mean time since RRSO was 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. In the premenopausal group, mean age at questionnaire completion was 62.7 years, compared to 67.0 years in the postmenopausal group (p-value <.001). Sixty-nine percent of women in the premenopausal-RRSO group carried a BRCA1/2 PV versus 63.8% in the postmenopausal RRSO group (p-value .40). In the premenopausal RRSO group, 59.7% of women had a history of breast cancer, compared to 58.2% in the postmenopausal group (p-value .73). Breast cancer treatment did not differ between the groups. HRT was more often prescribed to women in the premenopausal RRSO group (29.1%, versus 9.2% in the postmenopausal RRSO group; p-value <.001). The duration of HRT use was similar in both groups (mean 1.9 years).
Sexual activity and sexual functioning in women aged 60-70 years

In women aged 60-70 years, there was no difference in sexual activity between the groups (premenopausal RRSO 47.4% versus postmenopausal RRSO 48.9%, p-value .80). Among women who were sexually active (n=176), mean pleasure score in the premenopausal RRSO group was 8.6 (SD 3.7), versus 8.6 (SD 3.0) in the postmenopausal group (Figure 3a, p-value .80) (Answers to individual questions of the pleasure score are 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-value: .07) and women with a premenopausal RRSO more often had substantial discomfort than women with a postmenopausal RRSO (35.6% versus 20.9%, respectively, p-value .04) (Figure 3a, distribution of discomfort score Figure 3b). 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 to
31.1% in the postmenopausal RRSO group (p-value < .001) (Figure 4b). Also 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, results were similar: among women with a premenopausal RRSO 46.1% reported substantial complaints of vaginal dryness compared to 24.2% of women with a postmenopausal RRSO (p-value < .01) (Figure 4a).

[INSERT FIGURE 4 AROUND HERE]

[INSERT TABLE 3 AROUND HERE]

**Subgroup analyses in the entire premenopausal RRSO group**

**Timing of RRSO (before age 41 versus at ages 41-45 years)**

Among women with an early premenopausal RRSO (before age 41, n=151), 56.0% were still sexually active at time of questionnaire completion, compared with 60.9% in the late premenopausal RRSO group (RRSO at ages 41-45 years, n=348) (p-value .34). Women with an early premenopausal RRSO did not differ from women with a late premenopausal RRSO with respect to sexual pleasure or discomfort scores (Figure 3c). Complaints about vaginal dryness were also similar (Figure 4c); 42% of women with an early premenopausal RRSO reported substantial vaginal dryness compared to 49% in the late premenopausal RRSO group (p-value .27).

[INSERT FIGURE 5 AROUND HERE]

**Ever HRT-use versus never HRT-use in the premenopausal RRSO group**

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

Women with a premenopausal RRSO with and without a history of breast cancer

Within the premenopausal RRSO group we compared women with (n=297) and without a 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 age 46), compared to women with a postmenopausal RRSO (after age 54). After adjustment for age and breast cancer history, the proportion of sexually active women did not differ between the groups; at the age of 60-70 years 48% of women in the premenopausal RRSO group were still sexually active versus 45% in the postmenopausal RRSO group. Regarding sexual pleasure; the premenopausal and postmenopausal RRSO groups scored similarly, indicating equal pleasure with sexual activity. However, after adjustment for confounders such as age and breast cancer history, women with a premenopausal RRSO more often experienced substantial discomfort during sexual intercourse, due to more severe complaints of vaginal dryness. When comparing women with
RRSO before age 41 and RRSO at ages 41-45, there was no difference in mean discomfort scores or in 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 propose several possible explanations. Firstly, it is possible that women in our study experience 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. Secondly, 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. Thirdly, it is possible that we experienced a so-called “floor” effect in the scoring of the pleasure domain because the majority of respondent do not consider sex a very important part of their life. Lastly, it is possible that the high scores in sexual satisfaction and the lower scores in arousal have attenuated 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. However, women who used HRT at time of 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.\(^2\)\(^2\) 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,\(^2\)\(^3\) 52% of the 60-70 year old participants were not sexually active, which is comparable to the 54% in our sample in the same age category. As they used the Female Sexual Function Index rather than the SAQ, other comparisons with our results are not possible.
Previous studies on sexual functioning after RRSO had short follow-up (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, is the first to assess the long-term effects of a premenopausal RRSO on sexual functioning, and shows that, in the long run, pleasure with sexual activity is similar to that in women with a postmenopausal RRSO. However, women with a 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, as well as the comparison groups used; e.g. in some analyses women with a premenopausal RRSO were combined with women with a postmenopausal RRSO. Moreover, in previous reports mean age at 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, the majority of women (77.8%) never used HRT, this is 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 provides important information for clinicians counselling 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 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, 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, is 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 onwards, the national guideline for familial ovarian cancer strongly recommended RRSO for all women with BRCA PV, at the age of 35-40 years for BRCA1 PV and at ages 41-45 for BRCA2 PV carriers. Consequently, the majority of women (94.5%) with a postmenopausal RRSO was tested and underwent RRSO before 2007. To overcome this limitation, we performed analyses for women in the overlapping age range, 60-70 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 a premenopausal or postmenopausal RRSO. The HARMOny study invitation letter focused on potential effects of premenopausal RRSO on cardiovascular disease and bone health. A last concern may be that, despite the fact that we defined sexual activity to include non-coital sex and masturbation in the instructions for completing the SAQ, we cannot 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 pre- and postmenopausal RRSO groups.
Strengths of our study include the large sample size, providing sufficient power to perform several subgroup analyses. Additionally, by excluding women with RRSO at ages 46-54, we were able to make a more distinct evaluation of the differences in sexual health between women who underwent RRSO prior to 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. Also, and more generally, our study is one of the first to assess sexual functioning in a large group of women aged 60 or older.

Conclusions

In conclusion, more than 15 years after premenopausal RRSO, women experienced more severe complaints of vaginal dryness and more discomfort with sexual intercourse than women with a postmenopausal RRSO. However, this did not result in less pleasure with sexual activity. This knowledge can be integrated into pre-surgery counseling regarding expected sexual functioning after premenopausal RRSO.
Declarations

Ethics approval and consent to participate

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 AVL/NKI 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. Results will be disseminated through peer-reviewed publications and will be incorporated in follow-up guidelines.

Authors’ contributions

were involved in the conception and design of the study. LT, FvL, MB, EE, MM, MH and BHG drafted the manuscript. MB, JR, HvD, JdH, EvD, CM, BS, KG, LvdK, JC, MW, MA, KvE, IvdB, LB, CvA, EG, NA and AM were involved in the final version of the manuscript.

Funding

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References


Table 1. Characteristics of study participants

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Entire study population</th>
<th>Women aged 60-70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Premenopausal RRSO (n=499)</td>
<td>Postmenopausal RRSO (n=256)</td>
</tr>
<tr>
<td>Age at questionnaire completion (mean, SD)</td>
<td>60.0 (3.5)</td>
<td>70.2 (4.3) *</td>
</tr>
<tr>
<td>Age at RRSO (mean, SD)</td>
<td>41.7 (2.8)</td>
<td>58.4 (3.6) *</td>
</tr>
<tr>
<td>Time since RRSO (mean, SD)</td>
<td>18.3 (4.1)</td>
<td>11.9 (3.0) *</td>
</tr>
<tr>
<td>Pathogenic genetic variants†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1 germline mutation</td>
<td>241 (49.2%)</td>
<td>75 (29.4%) *</td>
</tr>
<tr>
<td>BRCA2 germline mutation</td>
<td>96 (19.6%)</td>
<td>95 (37.3%) *</td>
</tr>
<tr>
<td>Established non-carrier</td>
<td>153 (31.2%)</td>
<td>96 (33.3%)</td>
</tr>
<tr>
<td>Breast cancer (yes)</td>
<td>293 (59.0%)</td>
<td>166 (65.1%)</td>
</tr>
<tr>
<td>Breast cancer before RRSO</td>
<td>235 (84.8%)</td>
<td>146 (91.3%) *</td>
</tr>
<tr>
<td></td>
<td>Current users</td>
<td>Past users</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------------</td>
<td>------------</td>
</tr>
<tr>
<td>Breast cancer after RRSO</td>
<td>42 (15.2%)</td>
<td>14 (8.8%)</td>
</tr>
<tr>
<td>Treatment of breast cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>284 (97.6%)</td>
<td>159 (98.8%)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>222 (76.3%)</td>
<td>86 (52.4%)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>182 (62.5%)</td>
<td>95 (59.0%)</td>
</tr>
<tr>
<td>Endocrine therapy</td>
<td>106 (36.4%)</td>
<td>53 (32.9%)</td>
</tr>
<tr>
<td>Prophylactic mastectomy (yes)</td>
<td>300 (62.1%)</td>
<td>84 (34.6%)</td>
</tr>
<tr>
<td>HRT use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current user</td>
<td>26 (5.2%)</td>
<td>2 (.8%)</td>
</tr>
<tr>
<td>Past user</td>
<td>101 (20.0%)</td>
<td>27 (10.5%)</td>
</tr>
<tr>
<td>Never user</td>
<td>332 (66.5%)</td>
<td>210 (82.0%)</td>
</tr>
<tr>
<td>HRT duration in years (mean (SD))</td>
<td>2.2 (4.5)</td>
<td>1.4 (3.3)</td>
</tr>
<tr>
<td>Type of HRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tibolone</td>
<td>37 (29.1%)</td>
<td>2 (6.9%)</td>
</tr>
<tr>
<td>Estradiol/progestogen</td>
<td>30 (23.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Estradiol only</td>
<td>11 (8.7%)</td>
<td>2 (6.9%)</td>
</tr>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Vaginal estrogen</td>
<td>2 (1.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>47 (37.0%)</td>
<td>25 (86.2%)</td>
</tr>
<tr>
<td>BMI (mean, SD)</td>
<td>26.5 (5.0)</td>
<td>25.8 (4.5)</td>
</tr>
<tr>
<td>Hysterectomy (Yes) §</td>
<td>69 (16.2%)</td>
<td>53 (28.5%) *</td>
</tr>
<tr>
<td>Body Image (EORTC-BR23) (mean, sd)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic medication (yes) ¶</td>
<td>217 (43.5%)</td>
<td>139 (54.3%) *</td>
</tr>
</tbody>
</table>

* p-value < .05 Groups compared using independent samples t-test, Chi-squared test or Fishers exact test.
† All participants had a high familial risk of ovarian cancer. All women were tested for pathogenic variants, not all had a BRCA1/2 mutation.
‡ Established non-carriers include women from BRCA1/2 families who tested negative as well as women from a breast/ovarian cancer family who tested negative for the pathogenic variants tested in the Netherlands
§ Prophylactic mastectomy: bilateral or contralateral.
¶ In the Netherlands a hysterectomy is not standard of care when performing RRSO.
‖ European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire (questions 9-12) with higher scores indicating more problems with body image (range 0-100).
¶ Chronic medication use: any medication taken daily for cardiovascular risk factors, cardiovascular disease or chronic disease.
Abbreviations: RRSO: risk-reducing salpingo-oophorectomy; SD: standard deviation; BMI: body mass index; HRT: hormone replacement therapy in sexually active women.

Additional characteristics of the study population are provided in supplementary table 2.

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

<table>
<thead>
<tr>
<th>Total sexually active women aged 60-70 years (n= 171)</th>
<th>Total sexually active women in the premenopausal RRSO group (n= 276)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substantial discomfort* (n ( % )) for substantial discomfort</td>
<td>Substantial discomfort* (n ( % )) for substantial discomfort</td>
</tr>
<tr>
<td>Timing of RRSO</td>
<td>Timing of RRSO</td>
</tr>
</tbody>
</table>

*Substantial discomfort*
<table>
<thead>
<tr>
<th>Status</th>
<th>No (%)</th>
<th>RR  (95% CI)</th>
<th>Status</th>
<th>No (%)</th>
<th>RR  (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal</td>
<td>14 (20.9%)</td>
<td>1.00</td>
<td>Early premenopausal</td>
<td>33 (37.5%)</td>
<td>1.00</td>
</tr>
<tr>
<td>(RRSO ≥ 54 years)</td>
<td></td>
<td></td>
<td>(RRSO ≤ 40 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>37 (35.6%)</td>
<td>3.13</td>
<td>Later premenopausal</td>
<td>78 (41.5%)</td>
<td>0.97</td>
</tr>
<tr>
<td>(RRSO ≤ 45 years)</td>
<td></td>
<td>(1.04;9.36)</td>
<td>(RRSO 41-45 years)</td>
<td></td>
<td>(0.56;1.69)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>1.15</td>
<td>Age</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>History of breast cancer</td>
<td></td>
<td>(.98;1.35)</td>
<td>History of breast cancer</td>
<td></td>
<td>(.92;1.08)</td>
</tr>
<tr>
<td>No</td>
<td>21 (29.2%)</td>
<td>1.00</td>
<td>No</td>
<td>44 (35.8%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>30 (30.3%)</td>
<td>1.02</td>
<td>Yes</td>
<td>67 (43.2%)</td>
<td>1.32</td>
</tr>
<tr>
<td>Predictor</td>
<td>Odds Ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (continuous, per 1 kg/m² increase)</td>
<td>1.08 (1.00;1.16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BR23-body image (continuous, per 1 point more)</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>0.38 (0.55*10^-5; 0.27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (continuous, per 1 kg/m² increase)</td>
<td>NS</td>
</tr>
<tr>
<td>BR23-body image (continuous, per 1 point more)</td>
<td>1.01 (1.00;1.03)</td>
</tr>
<tr>
<td>Constant</td>
<td>0.64 (0.00;85.23)</td>
</tr>
</tbody>
</table>

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

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

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

<table>
<thead>
<tr>
<th>Timing of RRSO</th>
<th>Vaginal dryness in women aged 60-70 years (n=351)</th>
<th>Vaginal dryness in women with a premenopausal RRSO (n=483)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Substantial vaginal dryness* (n (%))</td>
<td>Substantial vaginal dryness* (n (%))</td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>1.06 (.97;1.16)</td>
<td>1.02 (.96;1.08)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>41 (31.1%)</td>
<td>61 (41.8%)</td>
</tr>
<tr>
<td>(RRSO ≥ 54 years)</td>
<td>1.00 (REF)</td>
<td>1.00 (REF)</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>103 (47.0%)</td>
<td>165 (49.0%)</td>
</tr>
<tr>
<td>(RRSO ≤ 45 years)</td>
<td>2.56 (1.40;4.68)</td>
<td>(0.75;1.77)</td>
</tr>
<tr>
<td></td>
<td>2.56</td>
<td>1.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of breast cancer</td>
<td>History of breast cancer</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------------</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>57 (40.1%)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>1.00 (REF)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>87 (41.6%)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>(0.67;1.62)</td>
<td></td>
</tr>
<tr>
<td>Use of chronic medication</td>
<td>NS</td>
<td>Use of chronic medication</td>
</tr>
<tr>
<td>No</td>
<td>63 (39.1%)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>81 (42.6%)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (continuous, per 1 kg/m² increase)</td>
<td>NS</td>
<td>BMI (continuous, per 1 kg/m² increase)</td>
</tr>
<tr>
<td>Constant</td>
<td>0.01 (0.00;4.07)</td>
<td>Constant</td>
</tr>
</tbody>
</table>
Vaginal dryness was assessed on a 5-point likert scale with higher scores indicating more vaginal dryness (FACT-ES).

* 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.

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

Figure 1. Participant Flowchart.

Number of participants enrolled, non-responders and number of women who declined participation. We have sent out regular reminders to women to complete the online questionnaire. We compare women with a premenopausal RRSO with women with a postmenopausal RRSO and secondly we compare within the premenopausal RRSO group women with an early premenopausal RRSO with women with a later premenopausal RRSO.

Figure 2. Proportion of sexually active women by age category at completion of questionnaire.

Age 55-59 years: Premenopausal RRSO n=267 of whom 180 sexually active, postmenopausal RRSO n= 0; Age 60-70 years: premenopausal RRSO n=226 of which 107 sexually active, postmenopausal RRSO n=142 of whom 70 sexually active; Age 71+ years: premenopausal RRSO n=6 of whom 2 sexually active, postmenopausal RRSO n= 114 of whom 32 sexually active

Figure 3 Mean sexual activity subscale scores and standard deviation

(a) Mean pleasure, discomfort and habit scores in women aged 60-70 years comparing premenopausal RRSO with postmenopausal RRSO. Range pleasure score 0 – 18. Range discomfort score 0 – 6. Range habit score 0-3 (b) Distribution of discomfort score in women aged 60-70 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.
Figure 4. Severity of complaints of vaginal dryness

(a) in total study population comparing women who were sexually active and women who were not sexually active (b) in women aged 60-70 years comparing premenopausal RRSO with postmenopausal RRSO (c) in women with a premenopausal RRSO comparing women with a RRSO before age 41 and women with a RRSO at ages 41-45 years.
DISTRIBUTION OF DISCOMFORT SCORE IN WOMEN AGED 60-70 YEARS

Discomfort Score
- Premenopausal RRSO (RRSO ≤ 45 YEARS) (N=104)
- Postmenopausal RRSO (RRSO ≥ 55 YEARS) (N=67)
Total number of women invited: 1311

- Premenopausal RRSO (RRSO ≤ 45 years of age):
  - Participants: 757 (57.7%)
  - Non-responder: 114 (15.1%)
  - Declined participation: 187 (33.8%)

- Postmenopausal RRSO (RRSO ≥ 54 years of age):
  - Participants: 554 (42.3%)
  - Non-responder: 165 (19.0%)
  - Declined participation: 187 (33.8%)

- Early premenopausal RRSO (RRSO ≤ 40 years of age):
  - Analysis of complete premenopausal RRSO group:
    - Completed online questionnaire: 499 (95.0%)
    - Did not yet complete online questionnaire: 26 (5.0%)
  - Aged between 60-70 years: 226 (45.3%)

- Late premenopausal RRSO (RRSO 41-45 years of age):
  - Analysis of overlapping ages:
    - Completed online questionnaire: 256 (97.7%)
    - Did not yet complete online questionnaire: 6 (2.3%)
  - Aged between 60-70 years: 142 (53.5%)
SEXUAL ACTIVITY QUESTIONNAIRE
MEAN SCORES (SD) IN WOMEN AGED 60-70 YEARS

<table>
<thead>
<tr>
<th></th>
<th>Pleasure score</th>
<th>Discomfort score</th>
<th>Habit score</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREMENOPAUSAL RRSO (RRSO ≤ 45 YEARS) (N=104)</td>
<td>8.6 (±1.5)</td>
<td>2.0 (±1.5)</td>
<td>1.8 (±0.8)</td>
</tr>
<tr>
<td>POSTMENOPAUSAL RRSO (RRSO ≥55 YEARS) (N=67)</td>
<td>8.6 (±1.5)</td>
<td>1.5 (±0.8)</td>
<td>1.8 (±0.8)</td>
</tr>
</tbody>
</table>
SEXUAL ACTIVITY QUESTIONNAIRE
MEAN SCORES (SD) IN THE PREMENOPAUSAL RRSO GROUP

<table>
<thead>
<tr>
<th>Score Type</th>
<th>Early Premenopausal RRSO (RRSO ≤ 40 years) (N=90)</th>
<th>Later Premenopausal RRSO (RRSO 41-43 years) (N=197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleasure score</td>
<td>9.1 ± 8.1</td>
<td>8.1 ± 8.1</td>
</tr>
<tr>
<td>Discomfort score</td>
<td>2.0 ± 2.3</td>
<td>2.3 ± 2.3</td>
</tr>
<tr>
<td>Habit score</td>
<td>1.7 ± 1.6</td>
<td>1.6 ± 1.6</td>
</tr>
</tbody>
</table>


**Severity of Vaginal Dryness According to Sexual Activity**

- **Not at All**: 40% Sexually Active (N=376) vs. 10% Not Sexually Active (N=340)
- **A Little Bit**: 18% Sexually Active vs. 12% Not Sexually Active
- **Somewhat**: 14% Sexually Active vs. 12% Not Sexually Active
- **A Fair Amount**: 18% Sexually Active vs. 16% Not Sexually Active
- **Very Much**: 10% Sexually Active vs. 12% Not Sexually Active

Number of participants: 716
SEVERITY OF VAGINAL DRYNESS IN PREMENOPAUSAL RRSO GROUP

- **NOT AT ALL**: Early 45% and Later 37%
- **A LITTLE BIT**: Early 15% and Later 13%
- **SOMewhat**: Early 14% and Later 9%
- **A FAIR AMOUNT**: Early 20% and Later 23%
- **VERY MUCH**: Early 13% and Later 12%

**EARLY PREMENOPAUSAL RRSO (RRSO ≤ 40 YEARS) (n=146)**

**LATER PREMENOPAUSAL RRSO (RRSO 41-45 YEARS) (n=337)**
### Severity of Vaginal Dryness in Women Aged 60-70 Years

<table>
<thead>
<tr>
<th>Severity Level</th>
<th>Premenopausal RRSO (n=219)</th>
<th>Postmenopausal RRSO (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>39%</td>
<td>51%</td>
</tr>
<tr>
<td>A little bit</td>
<td>14%</td>
<td>18%</td>
</tr>
<tr>
<td>Somewhat</td>
<td>12%</td>
<td>14%</td>
</tr>
<tr>
<td>A fair amount</td>
<td>24%</td>
<td>6%</td>
</tr>
<tr>
<td>Very much</td>
<td>11%</td>
<td>11%</td>
</tr>
</tbody>
</table>

*Note: The chart illustrates the percentage of women in different age groups experiencing varying levels of vaginal dryness.*