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ORIGINAL REPORT

The Impact of Hormone Replacement Therapy on Menopausal Symptoms in Younger High-Risk Women After Prophylactic Salpingo-Oophorectomy

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ABSTRACT

Purpose
Preventive health strategies for women at increased hereditary risk of ovarian cancer include gynecologic screening (GS) and/or prophylactic oophorectomy (PBSO). Hormone replacement therapy (HRT) is often prescribed to compensate for postsurgical endocrine deficiencies. This study examined the impact of HRT use on levels of endocrine symptoms and sexual functioning among premenopausal women who have undergone PBSO. Comparisons were made with similar women undergoing GS.

Patients and Methods
Questionnaire data on endocrine symptoms and sexual functioning were obtained from 450 premenopausal, high-risk women who had participated in this nationwide, cross-sectional, observational study.

Results
Thirty-six percent of women had undergone PBSO and 64% had opted for GS. In the PBSO group, 47% of the women were current HRT users. They reported significantly fewer vasomotor symptoms than nonusers ($P < .05$). However, compared with premenopausal women undergoing GS, oophorectomized HRT users were more likely to report vasomotor symptoms ($P < .01$). HRT users and nonusers reported comparable levels of sexual functioning. Compared with women in the GS group, oophorectomized HRT users reported significantly more sexual discomfort due to vaginal dryness and dyspareunia ($P < .01$).

Conclusion
Although HRT has a positive impact on surgically induced vasomotor symptoms, it may be less effective than is often assumed. Symptom levels remain well above those of premenopausal women undergoing screening, and sexual discomfort is not alleviated by HRT. Physicians need to provide younger high-risk women considering PBSO with realistic information about both benefits and drawbacks of this preventive strategy, including information about premature menopause and HRT.

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INTRODUCTION

Preventive health care recommendations for women at increased hereditary risk of ovarian cancer include periodic gynecologic screening (GS) and/or prophylactic bilateral salpingo-oophorectomy (PBSO). In the face of uncertain efficacy of the currently available screening techniques, including transvaginal ultrasonography and CA-125 serology,[1] and the established risk-reducing benefit of PBSO for ovarian and breast cancers,[2,3] carriers of *BRCA1/BRCA2* gene mutations are usually advised to undergo PBSO after the age of 35 years or after the completion of childbearing.[4]

Adverse effects associated with PBSO in premenopausal women include loss of fertility, immediate onset of menopause with vasomotor and urogenital symptoms,[5,6] and a decline in sexual interest and activity.[7] The management of surgically induced menopause requires strategies for alleviating the climacteric symptoms, and improving women's functioning and quality of life. Hormone-replacement therapy (HRT) is often prescribed at the time of surgery.[8]

HRT has proven to be highly effective in alleviating vasomotor symptoms (eg, hot flushes, sweats) and urogenital atrophy in women undergoing natural menopause.[8,9] Because of its androgenic properties, tibolone has shown to have additional

beneficial effects on sexual functioning.[10-12] Recent studies,[13-17] however, indicate that HRT use by healthy menopausal women is associated with increased risks of breast cancer and cardiovascular complications, and that these risks may overshadow the potentially beneficial effects on osteoporosis and colon cancer. Current recommendations call for short-duration HRT treatment for severe symptoms, and avoidance of long-term use for prevention of chronic health conditions.[18,19]

Only two studies have investigated post-PBSO menopausal symptoms and sexual functioning as part of a larger investigation of the psychosocial impact of prophylactic surgery.[20,21] In both studies, PBSO was found to be associated with the occurrence of menopausal symptoms. The results with regard to sexual functioning were inconsistent, with some evidence of sexual impairment in the study of Elit et al,[20] but not in the study of Fry et al.[21] Neither of these studies investigated endocrine symptoms and sexual functioning explicitly in relation to post-PBSO HRT use.

The primary focus of this report is on the impact of HRT use on the levels of endocrine symptoms and sexual functioning among premenopausal women who have undergone PBSO. Comparisons are made with premenopausal high-risk women undergoing GS.

PATIENTS AND METHODS

Participants and Procedures

This investigation was part of a larger, cross-sectional, observational study of psychosocial issues surrounding ovarian cancer prevention among high-risk women in the Netherlands. Study participants were recruited from the gynecology departments of eight hospitals. Women were eligible for the larger study if they were between 30 and 75 years of age, came from a hereditary breast/ovarian cancer family, and had sought gynecologic advice on preventive measures at one of the clinics between 1996 and 2001. Patients were excluded from participation if they had undergone oophorectomy as treatment for a medical condition, or had metastatic cancer or any other severe comorbidity. The current analysis was restricted to data of women who were premenopausal at the time of PBSO or were currently premenopausal (GS group). Premenopause was defined as having regular menses during the last 6 months or before PBSO. After surgery, women were prescribed standard doses of HRT (estrogen/progesterone or tibolone) administered either orally or transdermally.

Eligible women who had undergone PBSO or GS received an invitation letter by mail, an informed consent form, a questionnaire, and a postage-paid return envelope. If no response was received after 2 weeks, reminders by mail and telephone were used. Patients were classified as nonrespondents if they actively declined to participate, or if they could not be reached after multiple attempts. The study was approved by the institutional review boards of all participating hospitals.

Measures

The 18-item Functional Assessment of Cancer Therapy–Endocrine Symptoms (FACT-ES) was used to assess menopausal symptoms.[22] Occurrence of each symptom in the last 4 weeks is scored on a 5-point Likert-type scale, ranging from "not at all" to "very much." Item scores can be summed to obtain a scale score (range, 0 to 72), with lower values indicating more symptoms.

The Sexual Activity Questionnaire[23] was used to measure sexual functioning. It consists of three scales: pleasure (six items on desire, enjoyment, satisfaction, and current frequency of activities); discomfort (two items on vaginal dryness, pain and discomfort during penetration); and habit (frequency of sexual activity compared with the usual level). Lower scores represent poorer sexual functioning.

Medical and Sociodemographic Data

HRT use was determined on the basis of patient's self-report, confirmed by medical record audit. Sociodemographic and other medical data were obtained from the questionnaire and the medical records. These data included age, marital status, education, employment, menstrual and reproductive history, personal history of cancer and its treatments, DNA status, prevalence of breast/ovarian cancer among relatives, and prophylactic surgery. In the case of discrepancies between self-reported and medical record data, the latter were considered as the primary information source.

Statistical Analysis

Descriptive statistics were generated to characterize the sample in terms of sociodemographic and medical variables. Student's t tests and χ^2 tests were used to examine potential differences in the background characteristics of women who had undergone PBSO versus GS.

The study sample was divided into three groups according to the type of prevention and the current hormonal status: oophorectomized, current users and nonusers of HRT (PBSO HRT users and PBSO HRT nonusers), and premenopausal women undergoing GS. One-way analysis of covariance was used to test for group differences in endocrine symptoms and sexual functioning, controlling for possible confounders (age, DNA status, history of breast cancer, tamoxifen use, and prophylactic mastectomy). Among HRT users, the effect of the type of medication (estrogen/progesterone v tibolone) was also investigated.

In addition, individual symptoms of the FACT-ES scale were dichotomized (symptom present was considered to be a response in either of the two highest categories, "very much" and "quite a bit"). For each symptom, a multivariate logistic regression analysis was conducted to determine the significance of between-group differences, when controlling for potential confounders.

RESULTS

Study Sample

Of 1,205 high-risk women in the hospitals' databases, 1,084 were eligible for study participation (Fig 1). The reasons for ineligibility were oophorectomy carried out as treatment for a medical condition (n = 94), death (n = 23), metastatic cancer (n = 3), and severe psychiatric problems (n = 1). In total, 858 (79%) women returned completed questionnaires. Lack of interest (n = 137), poor health (n = 8), and emotional problems (n = 8) were the main reasons for nonparticipation. The data of 12 women had to be excluded: five women reported that the questionnaire was not applicable to their present situation, given that their cancer risk was found not to be increased based on DNA testing; five women had a high percentage (> 50%) of missing values; and two women had undergone an oophorectomy before 1996. There were no statistically significant differences between the respondents and nonrespondents in the type of ovarian cancer prevention and mean age (data not shown). Among the respondents, 450 premenopausal women were identified, of whom 164 (36%) had undergone PBSO. Data on menopausal status of nonrespondents were not available.

The background characteristics of the sample are shown in Table 1. Compared with the GS group, the PBSO group was significantly older, more likely to have been diagnosed with breast cancer, to be *BRCA1/2* mutation carriers, and to have undergone prophylactic mastectomy (all $P < .001$). At the time of assessment, 47% of the PBSO group reported current use of HRT, with the largest percentage taking estrogen/progesterone medications. HRT users were younger (45 v 47 years; $P < .05$) and had undergone PBSO at a younger age (41 v 44 years; $P < .01$), were less likely to have a history of breast

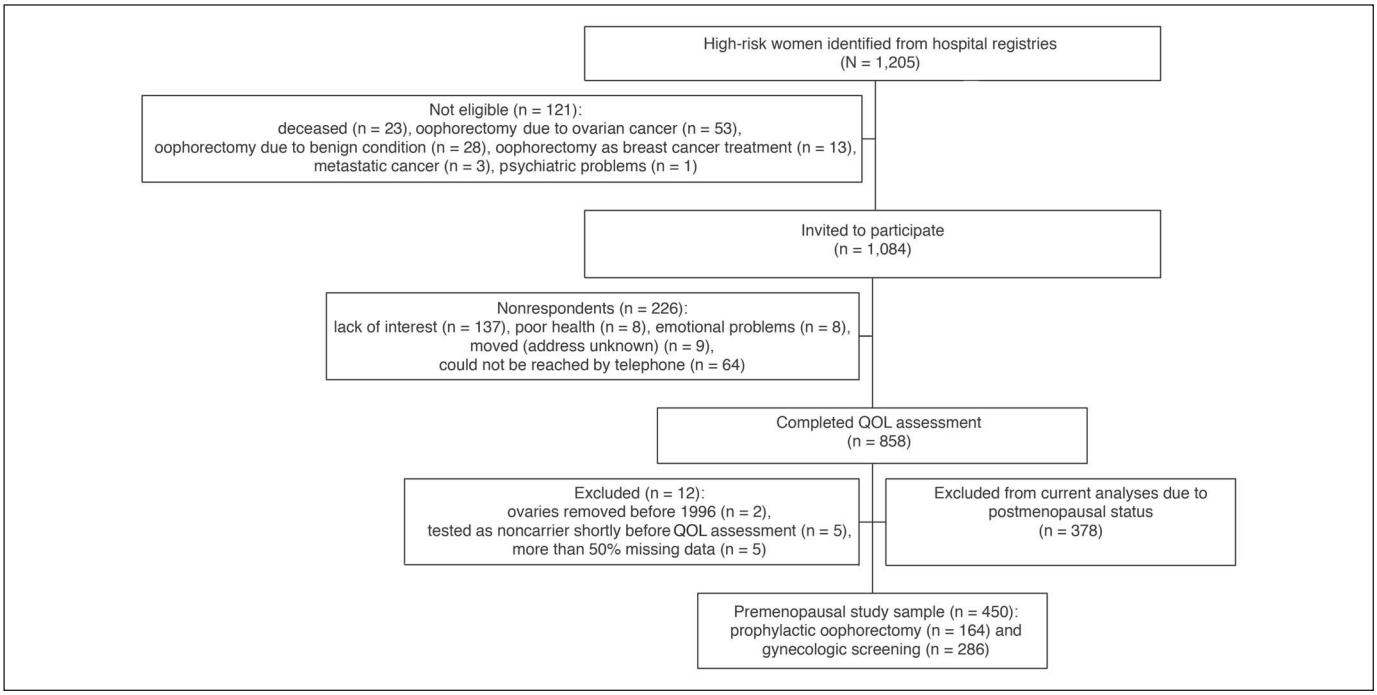

Fig 1. Study participant flow. QOL, quality of life.

cancer (17% *v* 47%; $P < .001$), and were more likely to have undergone prophylactic mastectomy (62% *v* 41%; $P < .01$) than nonusers. One fourth of the latter group reported having used HRT at some time postsurgery. Data on the reasons for HRT discontinuation were not available. The majority of current HRT users (82%) received a prescription for HRT at the time of PBSO, and reported having started HRT directly after surgery (72%) and being (highly) compliant with HRT use (99%; Table 1).

Endocrine Symptoms

Table 2 presents the mean FACT-ES scale scores and the individual symptom frequencies. As indicated by the mean scores, the PBSO HRT users group reported significantly fewer symptoms overall than the PBSO HRT nonusers group ($P < .05$). At the individual endocrine symptom level, significant between-group differences were found only for hot flushes, and cold and night sweats (all $P < .05$).

The PBSO HRT users group reported significantly more endocrine symptoms overall (FACT-ES scale scores) than the GS group ($P < .05$). Significant group differences were found in the frequency of all vasomotor symptoms, vaginal dryness, pain/discomfort during intercourse, and loss of interest in sex, with the PBSO HRT users group experiencing more problems (all $P < .01$).

Sexual Functioning

The majority of all study participants reported being sexually active (Table 3), and no significant differences between the groups were observed, after controlling for age, history of breast cancer, tamoxifen use, and prophylactic mastectomy. "Lack of interest in sex" or "having a bodily problem" were the most common reasons reported by oophorectomized women for not being sexually active (44% to 78%). Thirty-three percent of premenopausal women in the GS group reported being too tired or their partner being too tired as the main reason for their sexual inactivity (data not shown in the table).

The PBSO HRT users and PBSO HRT nonusers groups reported comparable levels of sexual functioning, as measured by the pleasure, discomfort, and habit scales of the Sexual Activity Questionnaire. Compared with the GS group, the PBSO HRT users group reported significantly more discomfort during sexual activities ($P < .01$).

Although the numbers were small (Table 1), we examined whether the type of HRT used differentially affected levels of endocrine symptoms and sexual functioning. No statistically significant differences were found between those who used estrogen/progesterone versus tibolone (data not shown in the table).

DISCUSSION

Many women from hereditary breast/ovarian cancer families consider PBSO or GS as a strategy for managing their increased risk of developing ovarian cancer. Although the risk reduction attributed to PBSO is largest in premenopausal women,[2,3,24] the resulting postoperative endocrine imbalance may affect functioning in several health domains. This report presents the results of a study that investigated the impact of PBSO on endocrine symptoms and sexuality among premenopausal, high-risk women, and the effect of HRT in alleviating these symptoms.

In the Netherlands, HRT is recommended as a means of alleviating vasomotor and sexual symptoms only to high-risk women who are premenopausal at the time of surgery. In clinical practice, it is generally recommended that HRT use begin immediately after PBSO, and be discontinued at the time of expected natural menopause (ie, at approximately 50 years of age).[4] There is currently no consensus about whether HRT use after oophorectomy contributes additionally to the already increased risk of breast cancer resulting from *BRCA1* or

Table 1. Sample Characteristics by Type of Ovarian Cancer Prevention

Characteristic	PBSO								
	Total PBSO Group (n = 164)		PBSO HRT User (n = 77)		PBSO HRT Nonuser (n = 87)		GS (n = 286)		
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	*P*
Current age, years									
Mean	46		45		47		41		
SD	6		5		7		6		.000*; .048†; .000‡
Range	34-59		34-51		34-59		30-54		
Marital status									.892*; .315†; .409‡
Married/cohabitating	139	85	68	88	71	83	243	85	
Unmarried/without partner	25	15	9	12	16	17	43	15	
Education level									.087*; .278†; .719‡
Primary school/lower level high school	30	18	11	13	19	22	34	12	
Middle level high school	85	52	41	53	44	51	138	48	
Advanced vocational/university	49	30	25	34	24	27	114	40	
Parity									.006*; .443†; .110‡
Nulliparous	22	13	12	16	10	11	69	24	
Primi-or multiparous	142	87	65	84	77	89	217	76	
DNA status									.000*; .135†; .000‡
BRCA 1/2 carrier	128	78	61	79	67	77	89	31	
Nonconclusive	16	10	4	5	12	14	51	18	
Not tested/other	20	12	12	16	8	9	146	51	
History of breast cancer	54	33	13	17	41	47	57	20	.000*; .000†;.547‡
Current use of tamoxifen	3	2	0	0	3	3	3	1	.359*; .100†; .462‡
Previous hysterectomy	7	5	4	5	3	3	1	0	.019*; .360†; .006‡
Prophylactic mastectomy	84	51	48	62	36	41	49	17	.000*; .007†; .000‡
Age at PBSO, years									
Mean	43		41		44		—		
SD	6		5		6				.004†
Time since PBSO, years									
Mean	2.8		3.1		2.5		—		
SD	2.2		2.3		2.1				.111†
Ever use of HRT	99	60	77	100	22	25	—		—
Current use of HRT	77	47	77	100	—		—		—
Type of HRT currently used									—
Estrogen/progesterone	—		54	70	—		—		
Tibolone	—		23	30	—		—		
Duration of HRT use in current users, years§	—				—		—		—
Mean			3.0						
SD			2.3						
HRT prescribed at the time of PBSO‖	—		63	82	—		—		—
HRT use started directly after PBSO‖	—		55	72	—		—		—
HRT used as prescribed‖									—
Always	—		69	90	—		—		
Most of the time	—		7	9	—		—		

Abbreviations: PBSO, prophylactic bilateral salpingo-oophorectomy; HRT, hormone-replacement therapy; GS, gynecologic screening; SD, standard deviation.
*Total PBSO group *v* GS group.
†PBSO HRT users group *v* PBSO HRT nonusers group.
‡PBSO HRT users group *v* GS group.
§Time interval between first postsurgical HRT use and current HRT use at the time of questionnaire assessment.
‖Self-reported data.

BRCA2 mutation carriership.[25] Recent studies[4,26] have suggested that decisions regarding HRT use should be based on quality-of-life considerations, rather than on life expectancy. Moreover, short-term HRT use does not negate the protective effect of PBSO on subsequent breast cancer risk in *BRCA1/2* mutation carriers.[26]

When deciding to undergo PBSO, younger women may expect that postsurgical HRT use will minimize if not entirely prevent menopausal symptoms, and that their functioning will return approximately to the presurgery level. In our study, 47% of oophorectomized women were currently using HRT. The results indicated that current

Table 2. Endocrine Symptoms Among HRT Users and Nonusers After Oophorectomy, and Premenopausal Women Undergoing Gynecologic Screening

Endocrine Symptom	Premenopausal PBSO HRT User (n = 77)* No. of Patients	%	Premenopausal PBSO HRT Nonuser (n = 87)* No. of Patients	%	Premenopausal GS (n = 286)* No. of Patients	%	P†
FACT-ES‡							.034§;.026‖
Mean	58.0		54.6		61.7		
SD	10.9		9.7		9.8		
Prevalence of selected symptoms							
Hot flushes	15	20	36	41	6	2	.004§;.000‖
Cold sweats	18	23	33	38	6	2	.034§;.000‖
Night sweats	19	25	34	39	20	7	.037§;.001‖
Vaginal discharge	4	5	1	1	26	9	.176§;.309‖
Vaginal itching/irritation	4	5	5	6	11	4	.865§;.445‖
Vaginal bleeding	3	4	1	1	26	9	.283§;.107‖
Vaginal dryness	10	13	21	24	6	2	.152§;.002‖
Pain/discomfort with intercourse	9	12	15	17	9	3	.133§;.008‖
Lost interest in sex	12	16	19	22	11	4	.350§;.002‖
Gained weight	13	17	16	18	26	9	.777§;.106‖
Lightheaded/dizzy	3	4	5	6	11	4	.585§;.610‖
Vomited	8	1	1	1	0	0	.959§;.994‖
Diarrhea	8	1	1	1	3	1	.508§;.516‖
Headaches	10	13	9	10	34	12	.617§;.826‖
Feel bloated	5	6	7	8	20	7	.673§;.480‖
Breast sensitivity/tenderness	2	2	4	5	23	8	.226§;.080‖
Mood swings	9	12	17	20	31	11	.174§;.955‖
Irritable	6	8	13	15	23	8	.160§;.726‖

Abbreviations: PBSO, prophylactic bilateral salpingo-oophorectomy; HRT, hormone-replacement therapy; GS, gynecologic screening; SD, standard deviation.
*Unadjusted percentages.
†All analyses were adjusted for age, history of breast cancer, tamoxifen use, and prophylactic mastectomy.
‡Possible score range: 0-72. Lower scores indicate more symptoms.
§PBSO HRT user *v* PBSO HRT nonuser.
‖PBSO HRT user *v* GS.

HRT use significantly reduced vasomotor symptoms, with prevalence rates being 14% to 21% lower among HRT users versus nonusers. Although these reductions are not trivial, previous studies of HRT use among women experiencing natural menopause have demonstrated larger reductions in vasomotor symptoms.[9] In addition, contrary to expectations based on clinical experience, no significant differences in the frequency of other endocrine symptoms (eg, vaginal dryness) were observed between HRT users and nonusers after controlling for possible confounders and type of medication. Surgical menopause may entail symptoms of higher severity for which commonly applied HRT may be less effective, given that it was originally designed to compensate for gradual endocrine losses in naturally menopausal women. This issue, however, needs to be addressed empirically.

Although HRT use does have a salutary effect on vasomotor symptoms in women with surgically induced menopause, it does not alleviate these symptoms entirely, as evidenced by the comparison

Table 3. Sexual Functioning Among Hormone-Replacement Therapy Users and Nonusers After Oophorectomy, and Premenopausal Women Undergoing GS

Sexual Functioning	Premenopausal PBSO HRT User (n = 77) Mean	SD	Premenopausal PBSO HRT Nonuser (n = 87) Mean	SD	Premenopausal GS (n = 286) Mean	SD	P*
Sexually active women, %	83		77		86		.713†; .693‡
SAQ scale scores§							
Pleasure	10.2	3.2	9.8	3.6	11.2	2.8	.700†; .154‡
Discomfort	4.8	1.5	4.4	1.7	5.5	1.0	.166†; .003‡
Habit	1.0	0.5	0.9	0.6	0.9	0.5	.451†; .713‡

Abbreviations: PBSO, prophylactic bilateral salpingo-oophorectomy; HRT, hormone-replacement therapy; GS, gynecologic screening; SD, standard deviation.
*All analyses were adjusted for age, history of breast cancer, tamoxifen use and prophylactic mastectomy. *P* values apply to the following comparisons:
†PBSO HRT users *v* PBSO HRT nonusers.
‡PBSO HRT users *v* GS.
§Scores available only for sexually active women. Lower scores indicate poorer sexual functioning.

with premenopausal women undergoing GS. It is commonly assumed that HRT use will virtually eliminate hot flushes.[27] The current findings indicate that oophorectomized HRT users continue to report significantly more vasomotor and other endocrine symptoms than the group of premenopausal women undergoing screening. The only previous study[21] that has compared the physical and psychosocial functioning of women undergoing PBSO versus GS found an overall trend for the surgical group (n = 29) to report more menopausal symptoms than the nonsurgical group (n = 28). However, it is unclear if that study adjusted statistically for current HRT use. In addition, the observed group differences were with regard to aches and pains, weight gain, and menstrual problems, but not vasomotor symptoms.

The majority of women in the current study reported being sexually active, and no significant differences were found in the level of activity between the oophorectomized HRT users, oophorectomized HRT nonusers, and women undergoing screening. However, oophorectomized women who were not sexually active attributed their inactivity significantly more frequently to decreased libido and bodily problems than did women in the screening group. HRT users and nonusers reported similar levels of sexual functioning, and HRT users reported significantly more discomfort (eg, vaginal dryness, dyspareunia) than women undergoing screening. These results are in line with other studies[6,20,28,29] that have reported impairments in sexual functioning due to surgically induced menopause, and sustained problems with libido, lubrication, and dyspareunia despite HRT use.[6,28] However, these studies included a more heterogeneous sample of women, including those who had undergone oophorectomy as a medical treatment. Two other studies of high-risk women who had undergone PBSO have reported that HRT may mitigate potential sexual problems.[21,30] However, these were single-center studies, the results of which were based on (qualitative) data derived from small samples.

Decreased androgen concentrations after PBSO may underlie sexual problems.[31] Some studies have reported that use of transdermal testosterone[32] or tibolone improves sexual function.[10,12,33] In our sample, none of the women were treated with testosterone. We did not observe any significant differences in sexual functioning among women using tibolone versus estrogen/progesterone. However, the sample size for this specific comparison was limited, with small numbers of tibolone users.

The strength of our study lies in its multicenter design, the large sample size, and the high response rate. We believe that the study sample is representative of high-risk women in the Netherlands. The main limitation of the study is its cross-sectional design, which does not allow for interpretation of causal relationships or detection of changes in endocrine symptom levels or sexual functioning over time due to the absence of a baseline (ie, presurgical) assessment. We are currently conducting a prospective, multicenter study with presurgical and follow-up assessment.

In addition, although we controlled for possible confounders in our statistical analyses, statistical adjustments cannot entirely rule out the possibility of indication bias, given that the study design was nonrandomized. Indication bias would suggest that the severity of menopausal symptoms would be decisive in whether or not to use HRT following PBSO. In clinical practice, the gynecologists from the participating hospitals typically prescribe standard doses of HRT preoperatively and recommend that women commence HRT use directly after PBSO, rather than waiting until menopausal symptoms occur. The majority of HRT users in our sample began using HRT directly after PBSO, and they were highly compliant with its use. Nevertheless, there are several reasons why one cannot entirely rule out the possibility of indication bias. First, for those women who were current HRT users, no information was available on whether their use had been continuous or intermittent during the period after surgery. Second, no data were available about the reasons why some women had discontinued postsurgical use of HRT. We would emphasize, however, that although indication bias may play some role in the comparisons made between HRT users and nonusers, it does not when comparing symptoms of oophorectomized HRT users with those of women undergoing gynecologic screening. Ultimately, one would want to investigate these issues in a randomized clinical trial. However, the feasibility of such a randomized clinical trial is questionable because it is likely that many eligible women would not want to be randomly assigned to HRT use or nonuse, or to a placebo group.

In conclusion, this study has documented relatively high levels of endocrine symptoms and impaired sexual functioning associated with PBSO. Although the efficacy of HRT in alleviating symptoms of natural menopause has been established in numerous randomized studies, our observational data suggest that HRT may be less effective in the case of surgically induced symptoms. Randomized studies are needed to determine the efficacy of HRT and testosterone supplementation in alleviating menopausal symptoms after PBSO, including dose-response issues. In addition, the role of nonhormonal medical treatments and psychosocial interventions in alleviating climacteric complaints merits further study. Ganz et al[34] have demonstrated that psychosocial interventions in combination with nonhormonal medications are a viable alternative to HRT among older breast cancer survivors suffering from menopausal symptoms. Possibly, younger oophorectomized women may also benefit from such interventions.

Physicians need to provide younger high-risk women considering PBSO with realistic and balanced information about both the benefits and possible drawbacks of this preventive strategy, including information about ovarian function, menopause, HRT, and psychosocial effects (eg, reduced cancer worries and lower risk perceptions).[30,35,36] Such balanced information will help women in making informed decisions about the optimal preventive health strategy.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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