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Effects of bilateral salpingo-oophorectomy on menopausal symptoms and sexual functioning among women with a *BRCA1* or *BRCA2* mutation

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HIGHLIGHTS

- *BRCA* mutation carriers experience a worsening of menopausal symptoms and sexual functioning with oophorectomy.
- This was particularly evident among those who underwent surgery prior to natural menopause.
- The use of HRT mitigated some but not all the adverse effects.
- Women who were premenopausal at surgery did not experience a decline in their quality of life.

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ABSTRACT

Introduction. Prophylactic bilateral salpingo-oophorectomy (BSO) is recommended at an early age to *BRCA* mutation carriers to prevent ovarian cancer. It is critical to evaluate the impact of BSO on non-cancer outcomes, including quality of life (QOL), menopausal symptoms and sexual functioning.

Methods. BRCA mutation carriers who elected to undergo a BSO completed three questionnaires prior to surgery and then again approximately one and three years following surgery which included: 1) medical history questionnaire, 2) Menopause-Specific Quality of Life Intervention questionnaire and 3) Sexual Activity Questionnaire. The change in quality of life, menopausal symptoms and sexual functioning before and after oophorectomy was determined using a paired *t*-test and stratified by menopausal status at surgery.

Results. We included 140 *BRCA* mutation carriers with an average follow-up of 3.5 years following BSO. Among 93 women who were premenopausal, oophorectomy was associated with an increase in menopausal symptoms (vasomotor, physical) ($P < 0.001$) and a decline in sexual functioning (discomfort, pleasure) ($P \leq 0.0001$), but had no impact on overall QOL ($P = 0.31$). HRT mitigated, but did not eliminate the adverse effects. Women who were postmenopausal at surgery (n = 47) experienced an increase in physical symptoms ($P = 0.03$) and a decline in sexual functioning (discomfort) ($P = 0.004$) and in overall QOL ($P = 0.04$).

Conclusions. This study demonstrates that 3.5 years after oophorectomy, *BRCA* mutation carriers experience a significant worsening of menopausal symptoms and a decline in sexual functioning, particularly among those who underwent surgery prior to natural menopause. The use of HRT mitigated some but not all the effects. Overall, women who were premenopausal at surgery did not experience a decline in their QOL.

1. Introduction

Women with a *BRCA1* or *BRCA2* mutation face a high lifetime risk of developing ovarian cancer and preventive bilateral salpingo-oophorectomy (BSO) (referred to as oophorectomy hereafter) is recommended prior to menopause [1]. Screening for ovarian cancer in high-risk women has not been shown to be reliable and currently surgical

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risk reduction is the most effective option [2]. Oophorectomy is currently recommended between the ages of 35 and 40 for *BRCA1* mutation carriers and between 40 and 45 for *BRCA2* mutation carriers [1,3]. Oophorectomy reduces the risk of developing ovarian cancer as well as all-cause mortality [4].

Despite the well-established reduction in cancer risk, oophorectomy induces surgical menopause and its associated risks and sequelae. The abrupt decline in circulating sex hormones (e.g., estrogen, testosterone, and progesterone) causes menopausal symptoms, including vasomotor symptoms and loss of libido, and is associated with a decline in cardiac and bone health, and perhaps in memory and attention [5–7]. This may be most apparent among those women who undergo surgery prior to natural menopause. Many of the side effects can be ameliorated by hormonal replacement therapy (HRT), but for women with a personal history of breast cancer, exogenous hormones are contraindicated due to fear of recurrence [8]. To date, there have been few prospective studies among women with a *BRCA* mutation who represent a unique population given their high rate of surgical menopause [reviewed in [9,10]]. Women undergoing preventive surgery experience reduced cancer-specific distress and a sustained level of overall quality of life [10].

In 2011, we, reported a worsening in menopausal symptoms and a decrease in sexual functioning one year after prophylactic oophorectomy among 114 women with a *BRCA1* or *BRCA2* mutation [11]. In the current study, we have revisited this cohort of women with an average of 3.5 years of post-surgery follow-up (and have increased the sample size) to evaluate to what extent these symptoms persisted beyond the first year following oophorectomy.

2. Materials and methods

2.1. Study population

This study population and data collection has previously been described in detail [11,12]. Eligible study subjects included women between the ages of 30 and 70 years who elected to undergo prophylactic salpingo-oophorectomy to reduce their risk of ovarian, fallopian tube or primary peritoneal cancer. Subjects were recruited through the University Health Network (Toronto, Canada) between Jan 2000 and May 2013. Women were eligible if they had: 1) a documented *BRCA1* or *BRCA2* mutation 2) at least one ovary intact, and 3) no personal history of any cancer other than breast cancer. Eligible participants were initially invited to participate by letter and then contacted by telephone one month prior to surgery. At this time, subjects provided written informed consent, and were asked to complete a medical release form, as well as three research questionnaires described in detail below. All women who completed the baseline questionnaires prior to surgery were re-contacted by mail to complete follow-up questionnaires at approximately one year and then again three years following completion of their baseline questionnaires. The institutional review boards of the host institutions approved the study.

2.2. Data collection

The study participants completed three questionnaires: 1) medical history questionnaire, 2) Menopause-Specific Quality of Life Intervention (MENQOL-Intervention) questionnaire and 3) Sexual Activity Questionnaire (SAQ).

The medical history questionnaire was designed specifically for this study and requested detailed information on reproductive history, height, weight, menopausal status, personal history of cancer, as well as medication use including HRT. Women were classified as premenopausal if she reported having a menstrual period in the year prior to surgery. Women who reported no menstrual period for one or more years due to previous hysterectomy, chemotherapy use, or natural menopause, classified as *postmenopausal*. *W*omen in the *menopausal transition/perimenopause* were included in the premenopausal. All women designated as *premenopausal* at baseline were confirmed to report having *surgical menopause* at follow-up. Subjects also reported on lifestyle factors including smoking status, alcohol intake, frequency and intensity of physical activity, and vitamin or supplement use.

The MENQOL-Intervention questionnaire assesses a total of 32 items divided into four domains: 1) vasomotor (three items; i.e., hot flashes, night sweats, sweating), 2) psychosocial (seven items; i.e., satisfaction with personal life, anxiety, memory, depression), 3) physical (19 items; i.e., difficulty sleeping, muscle aches, energy) and 4) sexual (three items; i.e., decrease in sexual desire, vaginal dryness, avoidance of intimacy) [13,14]. For each item, the woman was asked whether she experienced the problem in the past week, and if so, rate how much she was bothered by the problem using a 7-point Likert scale, from 0 (not bothered) to 6 (extremely bothered). For scoring, the responses were then transferred to an 8-point scale, from 1 (the subject did not experience the symptom) to 8 (the subject was extremely bothered). The total score for each of the four domains assessed by the MENQOL ranged between 1 and 8. We also included one additional question which asked 'How do you rate your overall quality of life?' and was based on a scale of 0 (poor) to 6 (excellent). For each domain, an increase in score indicates a worsening of symptoms and a decrease in score indicates an improvement.

The SAQ evaluates three domains: 1) sexual pleasure (desire, enjoyment and satisfaction), 2) discomfort (vaginal dryness and pain during penetration) and 3) habit (frequency of sexual activity compared to usual) [15]. The pleasure score is the sum of six items (range 0–18), the discomfort score is the sum of two items (range 0–6) and the habit score is derived from one item (range 0–3). A decline in these scores corresponds to a decrease in sexual functioning (i.e., decreased pleasure and frequency, more discomfort). Only women who reported being sexually active at baseline and at follow-up were included in this analysis.

2.3. Subject selection

In total, 258 women were contacted to participate in the study and 210 (81%) women completed the baseline questionnaire. Of the 210 women, 22 women were excluded; eight of these women were diagnosed with occult cancer at surgery; three women were deceased; five women did not confirm surgery date, and six women were diagnosed with cancer during follow-up resulting in a total of 188 potentially eligible women. In total, 140 (75%) out of the 188 women who met eligibility criteria, completed the baseline questionnaire and at least one follow-up questionnaire. Among the 48 women who did not complete at least one follow-up questionnaire, three women declined to participate and the others were lost to follow-up.

For the current analysis, subjects were censored if they were diagnosed with an incident breast cancer, if they had a breast cancer recurrence or did not complete a second follow-up. There were no incident cancers in this study population; however, there were five recurrences that occurred between completion of the first and second follow-up questionnaires. For these five women, only information from the baseline questionnaire and first follow-up was used. There was a total of 140 women who completed the baseline and first follow-up questionnaire and 113 who also completed the second follow-up questionnaire.

2.4. Statistical analysis

The goal of this analysis was to evaluate changes over a longer follow-up period post-surgery, i.e., between the baseline questionnaire completed prior to surgery and the second follow-up questionnaire, for each domain assessed by the two questionnaires, and thus, representing a longer follow-up period compared to our earlier report on this population [11]. For women who did not complete a second follow-up ($n = 27$), we used the information reported in the first follow-up. We also utilized data collected by the first follow-up and

evaluated changes between the first and second follow-up using a Student's *t*-test. The analysis was divided into two parts: 1) quality of life as assessed by the MENQOL-Intervention questionnaire and 2) sexual health as assessed by the SAQ. A paired *t*-test was used to evaluate the change in the score between the baseline questionnaire and the second follow-up questionnaire for all the domains evaluated by the questionnaires. For analyses stratified by menopausal status at the time of surgery and HRT use following surgery (premenopausal women only), the Student's *t*-test was used to evaluate differences in the scores between the subgroups. Generalized linear regression (PROC GLM) was used to adjust the baseline scores for age at surgery, previous breast cancer diagnosis and time between surgery and baseline questionnaire completion, the follow-up scores were further adjusted for HRT use, baseline score and time between surgery and follow-up questionnaire, and the change was additionally adjusted for the baseline score. All analyses were performed using SAS Version 9.1.3 (SAS Institute, Cary, NC, USA). All *P* values were based on two-sided tests and considered statistical significance if $P \leq 0.05$.

3. Results

3.1. Study population

The baseline characteristics of the women included in this study are summarized in Table 1. A total of 140 women were included in this study: 66 with a *BRCA1* mutation (47%) and 72 with a *BRCA2* mutation (52%) (Table 1). One woman (1%) had a mutation in both genes. All women had an oophorectomy; the mean age at oophorectomy was 46.7 years (range 35–75) and 66% of the women were premenopausal at the time of surgery. Of the 140 subjects, 113 (81%) completed two follow-up questionnaires and 27 (19%) only completed one follow-up questionnaire. Fifty women (36%) had a previous diagnosis of breast cancer and 20 (40%) were using tamoxifen or an aromatase inhibitor at the time of follow-up. On average, the women had been followed for 3.5 years from the dates of surgery (range 2.9–6.4 years). Very few women used HRT prior to surgery (6%), but 30% (n = 39–130; 10 missing information on HRT use) of the women had used HRT at some time after oophorectomy, including 11% (n = 5/45) of women with a previous breast cancer diagnosis and 40% (n = 34/85) of the patients without breast cancer. Most women used estrogen-alone HRT (89%) and some used a combination therapy (i.e., estrogen plus testosterone or estrogen plus progesterone)(11%).

3.2. Quality of life

Table 2 summarizes the scores from the MENQOL-Intervention questionnaire, at baseline and at the follow-up, as well as the change in the scores between the two time-points. The findings are stratified by menopausal status at the time of surgery and by HRT use following surgery (premenopausal women only).

There was no significant impact of oophorectomy on overall quality of life among premenopausal women ($P \leq 0.31$). Women who were postmenopausal at surgery experienced a significant decline in quality of life ($P = 0.04$) although the magnitude of change was not significantly different from that experienced by the premenopausal women ($P = 0.99$). At baseline, postmenopausal women reported significantly worse vasomotor symptoms (hot flashes, night sweats and sweating) compared to premenopausal women (2.96 vs, 1.88; $P = 0.005$). Baseline scores for sexual functioning (sexual desire, vaginal dryness, and avoidance of intimacy) were also worse, albeit not significantly, among postmenopausal women (3.32 vs. 2.13; $P = 0.06$). There was no significant difference in the baseline physical or psychosocial scores or any of the menopausal symptom scores experienced at the second follow-up, between the pre- and post-menopausal women ($P \geq 0.35$).

Among women who were premenopausal at surgery, there was a significant worsening in the vasomotor, physical and sexual domains

Table 1
Baseline characteristics of study subjects.

Variable	All subjects (n = 140)[b]	Premenopausal at surgery (n = 93)[b]	Postmenopausal at surgery (n = 47)[b]
Year of birth, mean (range)	1959.4 (1931.5–1974.0)	1962.3 (1952.9–1974.0)	1953.6 (1931.5–1967.3)
Age at surgery, mean (range)	46.7 (35–75)	43.8 (35–53)	52.4 (37–75)
Years between baseline and first follow-up, mean (range)	1.21 (0.59–3.14)	1.24 (0.59–3.14)	1.16 (0.84–1.97)
Years between first and second follow-up, mean (range)	2.29 (1.59–5.37)	2.31 (1.69–5.37)	2.24 (1.59–5.26)
Years between baseline and second follow-up, mean (range)	3.49 (2.86–6.38)	3.51 (2.92–6.38)	3.45 (2.86–6.23)
Surgery type, n (%)[a]			
Oophorectomy	23 (16.4)	12 (12.9)	11 (23.4)
Oophorectomy and Hysterectomy	117 (83.6)	81 (87.1)	36 (76.6)
Age distribution at surgery, n (%)			
35–39	18 (12.9)	16 (17.2)	2 (4.3)
40–44	45 (32.1)	36 (38.7)	9 (19.2)
45–49	41 (29.8)	34 (36.6)	7 (14.9)
50–54	18 (12.8)	7 (7.5)	11 (23.4)
55–59	7 (5.0)	0	7 (14.9)
60–75	11 (7.9)	0	11 (23.4)
Mutation type, n (%)			
BRCA1	66 (47.5)	49 (52.7)	17 (37.0)
BRCA2	72 (51.8)	43 (46.2)	29 (63.0)
BRCA1 + *BRCA2*	1 (0.7)	1 (1.1)	0
Missing	1	0	1
Height in inches, mean (range)	64.1 (56–70)	64.2 (56–70)	64.0 (58–69)
Weight in pounds, mean (range)	150.2 (95–245)	148.3 (104–245)	154.1 (95–210)
Body mass index in kg/m^2, mean (range)	25.7 (17.3–43.4)	25.4 (17.8–43.4)	26.4 (17.3–38.4)
Previous breast cancer diagnosis, n (%)			
No	90 (64.2)	70 (75.3)	20 (42.6)
Yes	50 (35.7)	23 (24.7)	27 (57.5)
HRT use at the end of follow-up			
No	91 (70.0)	50 (57.5)	41 (95.4)
Yes	39 (30.0)	37 (42.5)	2 (4.7)
Missing	10	6	4

[a] Oophorectomy refers to bilateral salpingo-oophorectomy.
[b] Woman missing mutation type coded was still included in the analysis.

Table 2
Menopausal symptoms prior to and following oophorectomy, by menopausal status at surgery and HRT use following surgery.

Domain[a]	Menopausal status at surgery			HRT use following surgery		
	Premenopausal (n = 93)	Postmenopausal (n = 47)	P^b	Non-users (n = 50)	Users (n = 37)	P^b
Vasomotor						
Baseline[c]	1.88 (1–6)	2.96 (1–8)	0.005	2.12 (1–6)	1.43 (1–5)	0.04
Follow-up[d]	3.27 (1–8)	3.00 (1–7)	0.44	3.61 (1–8)	2.70 (1–6)	0.09
Changes[e]	1.34 (−3–7)	0.04 (−3–3)	0.004	1.41 (−3–7)	1.27 (−2–5)	0.15
P for change[f]	<0.0001	0.83		<0.0001	<0.0001	
Physical						
Baseline[c]	2.25 (1–6)	2.68 (1–6)	0.35	2.43 (1–6)	2.00 (1–5)	0.27
Follow-up[d]	2.70 (1–7)	3.02 (1–6)	0.38	2.91 (1–6)	2.43 (1–5)	0.16
Changes[e]	0.48 (−2–3)	0.33 (−1–3)	0.70	0.52 (−2–3)	0.44(−2–2)	0.25
P for change[f]	<0.0001	0.03		0.002	0.006	
Sexual						
Baseline[c]	2.13 (1–8)	3.32 (1–8)	0.06	2.57 (1–8)	1.65 (1–6)	0.08
Follow-up[d]	3.54 (1–8)	3.70 (1–8)	1.00	4.17 (1–8)	2.84 (1–8)	0.12
Changes[e]	1.47 (−5–7)	0.39 (−4–6)	0.54	1.72 (−4–7)	1.19 (−5–6)	0.12
P for change[f]	<0.0001	0.19		<0.0001	0.005	
Psychosocial						
Baseline[c]	2.52 (1–7)	2.62 (1–6)	0.96	2.66 (1–6)	2.32 (1–7)	0.75
Follow-up[d]	2.79 (1–7)	2.85 (1–7)	0.58	2.87 (1–7)	2.51 (1–7)	0.48
Changes[e]	0.28 (−4–6)	0.23 (−3–2)	0.67	0.24 (−3–6)	0.19 (−4–4)	0.41
P for change[f]	0.07	0.57		0.17	0.23	
Quality of life						
Baseline[c]	4.72 (1–6)	4.45 (2–6)	0.17	4.43 (1–6)	5.03 (3–6)	0.04
Follow-up[d]	4.62 (0–6)	4.07 (0–6)	0.48	4.38 (0–6)	4.94 (2–6)	0.23
Changes[e]	−0.14 (−5–2)	−0.38 (−4–2)	0.99	−0.23 (−5–2)	−0.02 (−3–2)	0.39
P for change[f]	0.31	0.04		0.33	0.86	

[a] An increase in score corresponds to an increase in symptoms; 1 = no symptoms and 8 = extremely bothered by symptoms, *except* for the quality of life domain where an increase in score indicates an improved overall quality of life: 0 (poor) to 6 (excellent).
[b] Estimated using a Student's *t*-test.
[c] Adjusted for age at surgery, previous breast cancer diagnosis and time between surgery and baseline questionnaire across.
[d] Adjusted for age at surgery, previous breast cancer diagnosis, HRT use at follow-up and time between surgery and follow-up questionnaire.
[e] Adjusted for age at surgery, previous breast cancer diagnosis, HRT use at follow-up, baseline score and time between surgery and follow-up questionnaire.
[f] Estimated using a paired *t*-test.

(all $P < 0.0001$), but not in the psychosocial domain ($P = 0.07$). Women who were postmenopausal at surgery experienced a significant increase in the physical domain ($P = 0.03$) with no significant change in the vasomotor, sexual or psychosocial domains ($P \geq 0.19$), although this was based on only 47 women. Both women who did and did not initiate HRT use following surgery experienced a significant worsening in the vasomotor, physical and sexual symptoms ($P \leq 0.006$) with no significant impact of HRT use on psychosocial symptoms or overall quality of life. Although the overall change (worsening) in the menopausal symptoms experienced by HRT users and non-users did not differ for any of the MENQOL domains ($P \geq 0.12$), all four domains of menopausal symptoms were lower, albeit not all significantly, in the HRT users at baseline and at follow-up.

3.3. Sexual health

In total, 101 women (72%) reported being sexually active at baseline and at follow-up (79 premenopausal women and 29 postmenopausal women). The baseline, follow-up and change in the scores for the three domains derived from SAQ are summarized in Table 3, by menopausal status and by HRT use following surgery (among the premenopausal women only). There was a significant decline in the pleasure score (less pleasure) and discomfort score (more discomfort) among premenopausal women ($P \leq 0.0001$) and a significant decrease in discomfort among postmenopausal women ($P = 0.004$) with no significant impact of surgery on the habit (frequency) score irrespective of menopausal status ($P \geq 0.30$). There was no difference in the magnitude of change between baseline and the second follow-up in the pleasure and discomfort scores between the pre- and post-menopausal women ($P \geq 0.49$). The significant decline in the pleasure and discomfort scores was present for both women who did and did not use HRT ($P \leq 0.007$). There was no significant change in the habit domain by HRT use ($P \geq 0.35$). Interestingly, HRT users consistently experienced higher scores across the three sexual functioning domains at baseline and at the second follow-up compared to the non-users.

Supplemental Figs. 1–4 compare the mean values of the eight indices (i.e., menopausal symptoms, sexual functioning and overall quality of life) at baseline, at follow-up one and at follow-up two by menopausal status at surgery and by HRT use following surgery (premenopausal women only). The figures indicate that the magnitude of change experienced by the women shortly after surgery (first follow-up) is similar to what is observed in the longer follow-up period (second follow-up), suggesting immediate and sustained effects of surgical menopause ($P \geq 0.08$).

4. Discussion

This prospective study included 140 women with a *BRCA1* or *BRCA2* mutation and a mean follow-up of 3.5 years following preventive oophorectomy. Among the 93 women who were premenopausal, and thus experienced surgical menopause, we observed no decline in overall quality of life post-surgery, but there were declines in specific domains. There was a significant worsening in vasomotor, physical and sexual symptoms. For these domains, post-surgical levels were similar to those experienced by women who were postmenopausal at surgery. On average, symptoms were fewer among HRT users than non-users, but HRT use did not eliminate all the symptoms. Women who were postmenopausal at surgery experienced a significant decline in overall quality of life and physical symptoms; however, the magnitude of change was small.

Table 3
Sexual functioning prior to and following oophorectomy, by menopausal status at surgery and HRT use following surgery.

Domain[a]	Menopausal status at surgery			HRT use following surgery		
	Premenopausal (n = 79)	Postmenopausal (n = 29)	P^b	Non-users (n = 39)	Users (n = 34)	P^b
Pleasure						
Baseline[c]	13.05 (0–18)	10.73 (0–18)	0.20	11.63 (0–18)	14.34 (6–18)	0.006
Follow-up[d]	11.28 (0–18)	9.68 (0–18)	0.33	10.35 (0–17)	11.94 (3–18)	0.36
Changes[e]	−2.07 (−15–8)	−1.27 (−12–7)	0.49	−1.68 (−15–6)	−2.38 (−15–8)	0.75
P for change[f]	<0.0001	0.19		0.007	0.004	
Discomfort						
Baseline[c]	4.86 (0–6)	3.59 (0–6)	0.08	4.33 (0–6)	5.38 (0–6)	0.007
Follow-up[e]	3.19 (0–6)	2.22 (0–6)	0.53	2.68 (0–6)	3.62 (0–6)	0.30
Changes[e]	−1.73 (−6–6)	−1.35 (−5–4)	0.78	−1.71 (−5–4)	−1.76 (−5–1)	0.57
P for change[f]	<0.0001	0.004		0.0002	<0.0001	
Habit						
Baseline[c]	0.86 (0–3)	0.82 (0–3)	0.73	0.77 (0–2)	0.97 (0–3)	0.18
Follow-up[d]	0.77 (0–3)	0.71 (0–1)	0.85	0.71 (0–3)	0.85 (0–3)	0.05
Changes[e]	−0.09 (−2–3)	−0.08 (−3–1)	0.85	−0.06 (−1–3)	−0.12 (−2–3)	0.06
P for change[f]	0.30	0.62		0.69	0.35	

[a] A decrease in score indicates a decline in sexual functioning; pleasure (range 0–18); discomfort (range 0–6), habit (range 0–3).
[b] Estimated using a Student's *t*-test.
[c] Adjusted for age at surgery, previous breast cancer diagnosis and time between surgery and baseline questionnaire.
[d] Adjusted for age at surgery, previous breast cancer diagnosis, HRT use at follow-up and time between surgery and follow-up questionnaire
[e] Adjusted for age at surgery, previous breast cancer diagnosis, HRT use at follow-up, baseline score and time between surgery and follow-up questionnaire
[f] Estimated using a paired *t*-test

With respect to sexual functioning, we observed a significant decline in pleasure and discomfort after oophorectomy among premenopausal women. The effects were ameliorated somewhat with HRT use. Women who were postmenopausal at surgery only experienced a significant decline in discomfort. These findings suggest that there is a significant impact of early risk-reducing surgery on various menopausal symptoms and sexual functioning that are sustained several years post-surgery and not entirely restored to baseline (or pre-surgical levels) with HRT use. Importantly, with an additional 2.3 years of follow-up, the magnitude of change across all domains in the second follow-up was similar to what was observed in the first follow-up. Thus, the impact of oophorectomy appears to be immediate and sustained; however, there is no worsening of symptoms over time.

The current study is an extension of our earlier work. Finch and colleagues reported on the experiences of 114 *BRCA* mutation carriers before and one year following prophylactic oophorectomy [11]. We reported a significant worsening in vasomotor symptoms and a decline in sexual functioning among women who were premenopausal at surgery, but no impact of oophorectomy on the psychosocial and physical domains. The effects were significantly less among those women who used HRT; however, their levels did not return to baseline (pre-surgery) levels. Finch et al., only reported a significant decline in sexual function among postmenopausal women (n = 39) but in the current analysis we observed a decline in sexual functioning irrespective of menopausal status at surgery.

HRT use is prescribed to women to alleviate the symptoms associated with natural or surgical menopause; however, fewer than one-half of the women who were premenopausal at surgery initiated HRT use following surgery in our study population (n = 37; 43%). Although both HRT users and non-users equally experienced a worsening of menopausal symptoms and a decline in sexual functioning, HRT users reported less menopausal symptoms and better sexual functioning scores both at baseline and at follow-up, although the latter was based on a smaller number of women. We have recently published that use of estrogen-alone HRT after oophorectomy is not associated with an increased risk of breast cancer among women with a *BRCA1* mutation [16]. Given that the majority of these women also underwent hysterectomy, use of estrogen-alone HRT should be safely prescribed to alleviate symptoms associated with early surgical menopause. In contrast, combined estrogen and progestin formulations may be associated with an increased risk of breast cancer; however, data suggests that progesterone vs. synthetic progestins in older formulations may have less of an impact on breast cancer risk [17].

In a recent systematic review, Vermeulen et al., summarized findings from studies conducted among high-risk women undergoing risk-reducing salpingo-oophorectomy [10]. On the whole, surgical menopause was associated with sexual dysfunction and compromised menopause-specific quality of life compared to natural menopause, with no impact on overall quality of life or satisfaction with choice to undergo oophorectomy. Siyam and colleagues further summarized the data regarding the effect of HRT on various aspects of health following oophorectomy among *BRCA* mutation carriers [9]. With respect to quality of life, the effect of HRT were mixed with three studies showing an improvement in menopause-specific quality of life and three other studies showing no effect, although two of the latter studies were based on a small number of women in the oophorectomy group (range 38–51). Importantly, HRT consistently improved vasomotor symptoms and sexual functioning (in particular the discomfort domain) in most of the studies.

Women with a personal history of breast cancer bring an additional element of complexity in the care of this high-risk population given that treatment regimens (i.e., chemotherapy) have also been shown to impact the severity of menopausal symptoms and sexual functioning (reviewed in [18]). Furthermore, HRT is currently contraindicated in women with a personal history of disease [18]. In the current study, 23 of the 93 women (25%) who were premenopausal at surgery had a personal history of breast cancer; and five of these women (22%) used HRT following oophorectomy. None of the postmenopausal women with a prior diagnosis of breast cancer initiated HRT use following surgery. Given our small sample size and the multiple comparisons, we did not evaluate the impact of HRT on symptoms in an analysis stratified by personal history of breast cancer.

Our current study was not without limitations. We used self-administered questionnaires to collect information on menopausal symptoms, sexual functioning, breast cancer history and exogenous hormone use. Also, the use of self-reported data may have introduced error; however, any misclassification is anticipated to be non-differential. Furthermore, our sample size was small, precluding robust analyses in the subgroup analyses, including by personal history of breast cancer. Strengths of this study include the use of validated and

widely used questionnaires to capture detailed information on vasomotor symptoms and sexual functioning with demonstrated test-retest reliability [14,15,19,20], repeated measures from the same study participants allowing for paired analyses, and the relatively long follow-up period allowing for an evaluation of the long-term impact of surgical menopause on various outcomes. In addition, we were able to take into account baseline levels including time since oophorectomy in our adjusted analysis.

In summary, findings from this prospective analysis suggests that despite no impact on overall quality of life, premenopausal women undergoing preventive oophorectomy experience a significant decline in various domains and achieve levels experienced by women who are postmenopausal at surgery. Although not significantly, HRT did ameliorate many of the symptoms, and thus, HRT should be recommended to these women. Whether or not HRT may equally benefit postmenopausal women who experienced a significant change in physical symptoms, sexual functioning and overall quality of life warrants consideration. It is critical to continue to explore other long-term health consequences of oophorectomy, including cognitive function, cardiovascular health and bone mineral density in this high-risk population.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Author contribution

JK and SAN conceptualized this study. AF and EH were responsible for participant follow-up, data collection and data entry. PS performed statistical analysis. All authors participated in drafting and completing final approval of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2018.10.040.

References

[1] Genetic/Familial High-risk Assessment: Breast and ovariaN, http://www.nccn.org/professionals/ 2017.
[2] I.J. Jacobs, U. Menon, A. Ryan, et al., Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial, Lancet 387 (10022) (2016) 945–956.
[3] J. Kotsopoulos, J. Gronwald, B. Karlan, et al., Age-specific ovarian cancer risks among women with a BRCA1 or BRCA2 mutation, Gynecol. Oncol. 150 (1) (2018) 85–91.
[4] A.P. Finch, J. Lubinski, P. Moller, et al., Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation, J. Clin. Oncol. 32 (15) (2014) 1547–1553.
[5] S.S. Faubion, C.L. Kuhle, L.T. Shuster, W.A. Rocca, Long-term health consequences of premature or early menopause and considerations for management, Climacteric 18 (4) (2015) 483–491.
[6] L.T. Shuster, B.S. Gostout, B.R. Grossardt, W.A. Rocca, Prophylactic oophorectomy in premenopausal women and long-term health, Menopause Int. 14 (3) (2008) 111–116.
[7] W.A. Rocca, L. Gazzuola-Rocca, C.Y. Smith, et al., Accelerated accumulation of multimorbidity after bilateral oophorectomy: a population-based cohort study, Mayo Clin. Proc. 91 (11) (2016) 1577–1589.
[8] L. Holmberg, O.E. Iversen, C.M. Rudenstam, et al., Increased risk of recurrence after hormone replacement therapy in breast cancer survivors, J. Natl. Cancer Inst. 100 (7) (2008) 475–482.
[9] T. Siyam, S. Ross, S. Campbell, D.T. Eurich, N. Yuksel, The effect of hormone therapy on quality of life and breast cancer risk after risk-reducing salpingo-oophorectomy: a systematic review, BMC Womens Health 17 (1) (2017) 22.
[10] R.F.M. Vermeulen, M.V. Beurden, C.M. Korse, G.G. Kenter, Impact of risk-reducing salpingo-oophorectomy in premenopausal women, Climacteric 20 (3) (2017) 212–221.
[11] A. Finch, K.A. Metcalfe, J.K. Chiang, et al., The impact of prophylactic salpingo-oophorectomy on menopausal symptoms and sexual function in women who carry a BRCA mutation, Gynecol. Oncol. 121 (1) (2011) 163–168.
[12] A. Finch, K.A. Metcalfe, J. Chiang, et al., The impact of prophylactic salpingo-oophorectomy on quality of life and psychological distress in women with a BRCA mutation, Psychooncology 22 (1) (2013) 212–219.
[13] J.R. Hilditch, J. Lewis, A. Peter, et al., A menopause-specific quality of life questionnaire: development and psychometric properties, Maturitas 24 (3) (1996) 161–175.
[14] J.E. Lewis, J.R. Hilditch, C.J. Wong, Further psychometric property development of the Menopause-Specific Quality of Life questionnaire and development of a modified version, MENQOL-Intervention questionnaire, Maturitas 50 (3) (2005) 209–221.
[15] K. Thirlaway, L. Fallowfield, J. Cuzick, The Sexual Activity Questionnaire: a measure of women's sexual functioning, Qual. Life Res. 5 (1) (1996) 81–90.
[16] J. Kotsopoulos, J. Gronwald, B.Y. Karlan, et al., Hormone replacement therapy after oophorectomy and breast cancer risk among BRCA1 mutation carriers, JAMA Oncol. 4 (8) (2018 Aug 1) 1059–1065.
[17] A. Fournier, F. Berrino, F. Clavel-Chapelon, Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study, Breast Cancer Res. Treat. 107 (1) (2008) 103–111.
[18] R.J. Santen, C.A. Stuenkel, S.R. Davis, J.V. Pinkerton, A. Gompel, M.A. Lumsden, Managing menopausal symptoms and associated clinical issues in breast cancer survivors, J. Clin. Endocrinol. Metab. 102 (10) (2017) 3647–3661.
[19] K.B. Van Dole, R.F. DeVellis, R.D. Brown, M.L. Funk, B.N. Gaynes, R.E. Williams, Evaluation of the Menopause-Specific Quality of Life Questionnaire: a factor-analytic approach, Menopause 19 (2) (2012) 211–215.
[20] L. Atkins, L.J. Fallowfield, Fallowfield's Sexual Activity Questionnaire in women with without and at risk of cancer, Menopause Int. 13 (3) (2007) 103–109.