

Factors Associated with Altered Long-Term Well-Being After Prophylactic Salpingo-Oophorectomy Among Women at Increased Hereditary Risk for Breast and Ovarian Cancer

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Key Words. Quality of life • *BRCA* • Hereditary breast and ovarian cancer • Prophylactic oophorectomy • Menopause • Sexual function

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

- 1. Describe factors associated with decreased well-being after PBSO in order to prospectively identify patients at risk.
- 2. Provide pre-operative counseling and information to patients at risk of decreased well-being after PBSO.

CME This article is available for continuing medical education credit at <u>CME.TheOncologist.com</u>.

ABSTRACT

Background. Prophylactic bilateral salpingo-oophorectomy (PBSO) might alter several components of wellbeing, such as sexual functioning and endocrine symptoms, in women at high risk for hereditary breast and/or ovarian cancer, compared with the general population. We searched for factors associated with altered long-term well-being in this population (lower quality of life [QOL], altered sexual functioning, greater anxiety, more endocrine symptoms).

Methods. All high-risk women who had undergone

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Results. One hundred twelve of 175 women (64%) returned the completed questionnaires at a mean duration (standard deviation) of 6.0 (5.1) years after PBSO. QOL

INTRODUCTION

Women carriers of a *BRCA1* or *BRCA2* gene mutation have a substantially higher risk for breast and/or ovarian cancer. Prophylactic bilateral salpingo-oophorectomy (PBSO) is the main preventive health strategy in these patients. Its objective is to reduce the risk for both ovarian and breast cancer [1]. PBSO reduces ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers by 79% and breast cancer risk by 51% [2]. Risk reduction is effective whatever the *BRCA* mutation or history of previous breast cancer [3]. Furthermore, despite previous discussions regarding the potential long-term health consequences of early menopause [4], PBSO was recently clearly shown to reduce all-cause mortality by 60%, breast cancer-specific mortality by 56%, and ovarian cancer-specific mortality by 79% [3].

It has been reported that PBSO does not affect overall quality of life (QOL) but might alter sexual functioning and increase several endocrine symptoms in women having undergone the procedure, compared with the general population [5]. In contrast, favorable effects of PBSO in terms of lower anxiety levels and a low perceived cancer risk have been reported [5]. However, data are lacking concerning risk factors for altered results after surgery. Identifying women likely to experience a lower overall well-being after PBSO could potentially facilitate preoperative counseling and pre- or postoperative management. For this purpose, we selected both physical determinants and factors that could potentially influence their psychological well-being or worries about cancer from the available literature [5–8].

The objective of this study was therefore to search for factors associated with long-term altered well-being, namely, lower QOL, altered sexual functioning, greater anxiety, and more endocrine symptoms after PBSO. was positively influenced by two baseline factors: a high educational level and occupying an executive position. However, younger age at PBSO was associated with lower social functioning and greater anxiety. At the time of the study, practicing a sport and the avoidance of weight gain ($\geq 10\%$) were highly related to QOL, sexual pleasure, endocrine symptoms, and anxiety in the univariate analysis and predictive of better QOL and lower anxiety in the multivariate analysis.

Conclusions. Younger women and women with a low educational level and no occupation appear to be at higher risk for altered long-term well-being. After surgery, practicing a sport and stable weight may help maintain overall well-being. *The Oncologist* 2011;16:1250–1257

METHODS

Population

All women who had undergone PBSO at a single institution during the past 15 years because of a hereditary risk for breast or ovarian cancer were invited to participate in the study. Information letters were sent out offering them the possibility of accepting or declining participation in the study. If they accepted, they received anonymous questionnaires and a postage-paid return envelope. They were first asked general questions to evaluate their socioeconomic level, physical activity, menopausal status, and marital status before and after PBSO. Medical data were retrieved from hospital medical records. To assess generic QOL, the French version of the Cancer Quality of Life Questionnaire C30 (QLQ-C30) of the European Organization for Research and Treatment (EORTC) was used. The Sexual Activity Questionnaire (SAQ) was used to measure sexual functioning [9, 10]. Endocrine symptoms were evaluated by the Endocrine Symptom subscale of the Functional Assessment of Cancer Therapy questionnaire (FACT-ES) [11]. The level of anxiety was evaluated by the State-Trait Anxiety Inventory (STAI) [12].

Statistical Analysis

Descriptive statistics (frequencies, means, and standard deviations [SDs]) were generated to characterize the sample in terms of sociodemographic and medical variables. Before the analysis, we selected 19 clinically relevant variables from previous articles [5–8] and from sociodemographic questionnaires as factors potentially associated with "poor" postoperative results. Continuous variables were dichotomized a priori at the median. These variables were either before surgery (baseline factors) or at the time of the study (current status). Before surgery, vari-

	n	Percentage	Mean	Range
At surgery (baseline characteristics)	1			
Age, yrs $(n = 99)$			48	35-74
Main occupation $(n = 111)$				
Active	66	59%		
Retired	12	11%		
Without	32	29%		
Student	1	1%		
Education level ($n = 111$)				
<high graduate<="" school="" td=""><td>45</td><td>40%</td><td></td><td></td></high>	45	40%		
≥High school graduate	66	60%		
Married or in a couple $(n = 112)$				
Yes	94	84%		
No	18	16%		
n of children ($n = 112$)			2	0–5
0	10	9%		
≥1	102	91%		
Menopausal status ($n = 111$)				
Yes	53	48%		
No	58	52%		
Age at menopause, yrs ($n = 53$)			46	32-55
Antihormonal treatment $(n = 112)$				
Yes	22	20%		
No	88	80%		
Height, cm $(n = 110)$			162	139–173
Weight, kg ($n = 104$)			61	45–95
BRCA mutation $(n = 112)$				
BRCA1	55	49%		
BRCA2	37	33%		
None	20	18%		
Personal history of breast cancer $(n = 112)$				
Yes	86	77%		
No	26	23%		
Previous mastectomy ($n = 112$)				
Yes	56	50%		
No	56	50%		
Sexual activity ($n = 111$)				
Yes	89	80%		
No	22	20%		
Frequency (per month)	78		6	1-20

ables were age (\geq 50 years or <50 years), main occupation, educational level, professional function (executive or not), childbearing history, marital status, menopausal status, antihormonal treatment, hormone replacement therapy, body mass index (\geq 25 kg/m² or <25 kg/m²), sexual activity, presence of a *BRCA* mutation (none, *BRCA1*, or *BRCA2*), personal history of breast cancer, and history of mastec-

	п	Percentage	Mean	Range
t the time of the study				
Main occupation $(n = 111)$				
Active	66	59%		
Retired	32	29%		
Without	12	11%		
Student	1	1%		
Executive occupation ($n = 108$)				
Yes	60	56%		
No	48	44%		
Married or in a couple $(n = 112)$				
Yes	90	80%		
No	22	20%		
Practice sport ($n = 112$)				
Yes	67	60%		
No	45	40%		
<i>n</i> hours per month			12	2-60
<8 hours/month	28	42%		
\geq 8 hours/month	39	58%		
Practice hobbies $(n = 109)$				
Yes	78	72%		
No	31	38%		
<i>n</i> hours per month			25	0-120
Antihormonal treatment $(n = 112)$				
Yes	18	16%		
No	94	84%		
Hormone replacement therapy $(n = 112)$				
Yes	6	5%		
No	106	95%		
Sexual activity $(n = 108)$				
Yes	59	55%		
No	49	45%		
Frequency (per month)			5	0–15
Weight $(n = 111)$			64	46–97
Declared weight gain $\ge 10\%$ (<i>n</i> = 103)				
Yes	19	18%		
No	84	82%		
Under any medical treatment— no cancer $(n = 112)$				
Yes	38	34%		
No	74	66%		
Type ($n = 112$)				
Antidepressant	17	15%		
Hot flash treatment	10	9%		
Diabetes or high blood pressure treatments	17	15%		

tomy. At the time of the study, variables were current age (\geq 50 years or <50 years), marital status, practice of hob-



Variable	Mean	SD	Median
Physical functioning $(n = 111)$	87	15.2	93
Role functioning $(n = 110)$	88	20.0	100
Emotional functioning ($n = 109$)	72	23.0	75
Cognitive functioning $(n = 109)$	77	22.8	83
Social functioning $(n = 109)$	86	24.1	100
Global health status/QOL $(n = 109)$	68	20.8	67
Fatigue ($n = 111$)	27	24.1	22
Nausea/vomiting ($n = 109$)	3	12.0	0
Pain $(n = 111)$	17	23.2	0
Dyspnea ($n = 110$)	15	23.3	0
Insomnia ($n = 111$)	41	35.0	33
Appetite loss ($n = 111$)	9	20.7	0
Constipation ($n = 109$)	15	25.4	0
Diarrhea ($n = 108$)	7	19.4	0
Financial problems $(n = 108)$	8	23.7	0

bies (no, yes <20 hours per month, yes ≥ 20 hours per month), practice of sport (no, yes <8 hours per month, yes ≥ 8 hours per month), declared weight gain $\geq 10\%$ since PBSO, and interval between surgery and questionnaire (≥ 4 years or <4 years). Outcome variables were selected a priori: the QLQ-C30 contains 30 items combined to derive 15 scales according to the EORTC guidelines. We focused on eight scales: five functional scales (physical, role, emotional, cognitive, and social functioning), two symptom scales (fatigue and insomnia), and the global health status/ QOL. The scales' range is 0-100, with high scores corresponding to a healthy/high status for the global and functional scales, but to a high level of symptoms for the symptom scales. The EORTC SAS® program (SAS Institute Inc., Cary, NC) was used to score the QLQ-C30 items. The four SAQ dimensions and scores recommended by Fallowfield were retained (pleasure, discomfort, habit, and fatigue). Thus, a total of 14 criteria (the above-mentioned 12 items plus the FACT-ES menopause symptoms and STAI A anxiety item) were considered a priori and analyzed in relation to the 19 variables described above.

Univariate logistic analysis was used to identify factors associated with altered outcomes (defined as binary variables: worst quartile versus three other quartiles). A multivariate logistic regression analysis was conducted on factors that were significant in the univariate analysis. All *p*-values resulting from the logistic analyses are derived

Variable	n	%	Mean	SD	Median
Sexual activity $(n = 108)$					
Yes	59	55%			
No	49	45%			
Reasons for no sexual inactivity $(n = 48)$					
No partner	15	31%			
Fatigue	13	27%			
Fatigue of the partner	5	10%			
Not interested in sex	20	42%			
Partner not interested in sex	7	15%			
Physical problem	18	38%			
Physical problem of the partner	6	13%			
Other	16	33%			
Characteristics of sexual activity					
Pleasure $(n = 59)$			10.5	4.5	11
Discomfort ($n = 59$)			2.8	2.2	3
Habit $(n = 58)$			0.9	0.5	1
Fatigue $(n = 58)$			2.4	0.8	3

from χ^2 tests. All reported *p*-values are two-sided; *p*-values <1% were considered significant to take into account the multiplicity of tests. Analyses were performed with SAS[®], version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Among 175 women to whom questionnaires were sent in March 2009, 112 completed and returned the questionnaires by September 2009 (64%). PBSO had been performed via a laparoscopic approach in 99 women (88%) and via a laparotomy in 13 women (12%). The mean (SD) interval since PBSO was 6.0 (5.1) years. The mean age at PBSO was 48 (35–74) years. Fifty-five women (49%) were *BRCA1* carriers, 37 (33%) were *BRCA2* carriers, and 20 (18%) had no identified mutation. Eighty-six women (77%) had a personal history of breast cancer, 56 (50%) had previously undergone a mastectomy, and 23 (21%) had previously undergone a prophylactic bilateral mastectomy. The characteristics of women just before PBSO and at the time of the study are summarized in Table 1.

Descriptive Analysis: QOL, Sexual Functioning, Anxiety, and Endocrine Symptoms

The results of the QLQ-C30 are reported in Table 2. Over-

Symptoms, n (%)	Not at all	A little bit	Somewhat	Quite a bit	Very much
Vasomotor symptoms					
Hot flashes $(n = 106)$	43 (41)	11 (10)	25 (24)	18 (17)	9 (8)
Cold sweats $(n = 104)$	77 (74)	8 (8)	7 (7)	10 (10)	2 (2)
Night sweats $(n = 105)$	53 (50)	13 (12)	13 (12)	16 (15)	10 (10)
Gynecologic symptoms					
Vaginal itching/discharge ($n = 106$)	84 (79)	8 (8)	9 (8)	2 (2)	3 (3)
Vaginal irritation ($n = 107$)	67 (63)	15 (14)	14 (13)	8 (7)	3 (3)
Vaginal bleeding or spotting $(n = 107)$	98 (92)	4 (4)	3 (3)	1(1)	1(1)
Vaginal dryness ($n = 105$)	37 (35)	4 (4)	14 (13)	18 (17)	32 (30)
Breast sensitivity/tenderness ($n = 104$)	66 (63)	5 (5)	21 (20)	7 (7)	5 (5)
Pain or discomfort with intercourse ($n = 99$)	52 (53)	5 (5)	15 (15)	11 (11)	16 (16)
Lost interest in sex $(n = 104)$	34 (33)	5 (5)	22 (21)	15 (14)	28 (27)
Gastrointestinal symptoms					
Weight gain $(n = 105)$	51 (49)	5 (5)	19 (18)	13 (12)	17 (16)
Bloated feeling $(n = 103)$	81 (79)	5 (5)	6 (6)	6 (6)	5 (5)
Nausea ($n = 104$)	89 (86)	7 (7)	5 (5)	2 (2)	1(1)
Diarrhea ($n = 107$)	85 (79)	9 (8)	10 (9)	2 (2)	1 (1)
Neuropsychological symptoms					
Lightheaded (dizzy) feeling $(n = 107)$	73 (68)	13 (12)	15 (14)	4 (4)	2 (2)
Headaches ($n = 107$)	49 (46)	17 (16)	25 (23)	11 (10)	5 (5)
Mood swings $(n = 107)$	36 (34)	17 (16)	27 (25)	17 (16)	10 (9)
Irritability $(n = 107)$	29 (27)	19 (18)	30 (28)	20 (19)	9 (8)

all, global and specific QOL was not lower than the EORTC standard. The results of the SAQ are reported in Table 3. Fifty-nine patients (55%) were sexually active. The first reason explaining the sexual inactivity of the other 45% was a lack of interest in sex (42%). Long-term assessment of endocrine symptoms revealed a mean score of 18.2 (0–48). The most frequent complaints were vaginal dryness (47%) and loss of interest in sex (41%), as detailed in Table 4. Major vasomotor symptoms (quite a bit and very much) were reported by 25% of the women. The mean anxiety level score was 41.2 (20–73), which is considered a low anxiety level. The anxiety level was very low for 33%, low for 31%, intermediate for 20%, high for 13%, and very high for 4% of the women.

Factors Associated with QOL, Sexual Functioning, Anxiety, and Endocrine Symptoms

Baseline Factors

A high educational level (p = .01) and occupying an executive position (p = .01) at PBSO positively influenced the global health status (Table 5A). A younger age at PBSO

was specifically associated with lower social functioning (p = .007) and greater anxiety (p = .01). None of the 10 other baseline factors tested were significantly associated with QOL parameters, including the *BRCA* status and a history of breast cancer. For example, a trend toward lower physical functioning and social functioning in the QLQ-C30 questionnaire was observed for women with a history of breast cancer, but this was not statistically significant (p = .04 and p = .06, respectively). A history of mastectomy did not influence sexual pleasure (p = .9) or social functioning (p = .03).

Current Factors

Practicing a sport at the time of the study appeared to be highly related to a better global health status (p = .004), physical functioning (p = .01) and emotional functioning (p = .001), as well as greater sexual pleasure (p = .007), and less anxiety (p = .006) (Table 5B). Weight gain was associated with a lower global health status (p = .004), greater anxiety (p = .01), and greater endocrine symptoms (p = .0002). Practicing hobbies at the time of the study was associated with less anxiety (p = .01).



Table 5. Relationship between well-being scales and factors measured at the time of diagnosis and at the time of scale evaluation for baseline factors (A) and for current factors (B)

					A. Ba	seline fact	ors							
Scale	Age (≥50)	Occupation status (active)	Education level (≥high school)	Professional executive function	Childbearing history		Menopausal status (yes)				Sexual activity	BRCA mutation	Personal history of breast cancer	Previous mastectom
QOL: PF													↑ .04	
QOL: RF								↑ .05						
QOL: EF														
QOL: CF	↓ .07	↓ .08	↑ .02			↓ .06								
QOL: SF	↓ .007												↑.06	↑ .03
QOL: QL			↓ .01	↓ .01										
QOL: FA														
QOL: SL						↓ .07								
SAQ: Pleasure												↑ .04		
SAQ: Discomfort														
SAQ: Habit														
SAQ: Fatigue	↓ .01													
FACT	↓ .03								î	.04				↑ .08
STAI	↓ .01							↑ .05						
					B. Cu	rrent fact	ors							
Scale		Age (≥50)		rital status uple)	Practic hobbies		Practice sport		Veight g BSO ≥		nce		y surgery-0 yrs)	questionnair
QOL: PF							↓ .01	î	.03					
QOL: RF								Î	.06					
QOL: EF							↓ .001							
QOL: CF		↓ .07												
QOL: SF		↓ .03												
QOL: QL							↓ .004	î	.004					
QOL: FA		↓ .05												
QOL: SL			\downarrow .	.01										
SAQ: Pleasure		↑ .07					↓ .007							
SAQ: Discomfort							↓ .02							
SAQ: Habit								Î	.09					
SAQ: Fatigue		↓ .06										↓.()6	
FACT		↓ .09						Î	.0002					
STAI					↓ .01		↓ .006	Î	.01					

In each cell, a two-sided *p*-value from a χ^2 test is reported (if <.10) together with an arrow indicating the direction of the risk for having an altered outcome: \uparrow represents a higher risk (negative influence) whereas \downarrow represents a lower risk (positive influence). Values in bold indicate a *p*-value < .01.

Abbreviations: CF, cognitive functioning; EF, emotional functioning; FA, fatigue; FACT, Functional Assessment of Cancer Therapy; PBSO, prophylactic bilateral salpingo-oophorectomy; PF, physical functioning; QL, global health status/QOL; QOL, quality of life; RF, role functioning; SAQ, Sexual Activity Questionnaire; SF, social functioning; SL, insomnia; STAI, State-Trait Anxiety Inventory.

Multivariate Analysis

Because only QOL and anxiety had more than one statistically significant (p < .01) correlation, multivariate analyses were performed exclusively for these two scales. In the multivariate analyses, sport and the absence of weight gain were both highly predictive of a better global health status (p = .008 and p = .005, respectively) and lower anxiety (p = .007 and p = .007, respectively). Furthermore, >8 hours of sport was also significantly associated with a better global health status and lower anxiety than with <8 hours of sport (p = .02 and p = .01, respectively) (Table 6).

DISCUSSION

In this long-term observational study among women who had undergone PBSO for a high risk for breast and ovarian cancer, overall QOL results did not differ from the standard

	Quality of	f life	Anxiet	У
Criteria at the time of the study	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
Sport		.008		.007
Sport (<8 hours versus none)	0.2 (0.1–0.9)	.02	0.3 (0.1–1.2)	.01
Sport (≥8 hours versus none)	0.2 (0.1–0.7)		0.2 (0.05–0.6)	
Weight gain ≥10%	3.9 (1.7-16.6)	.005	5.3 (1.6-17.7)	.007

reference EORTC results [5, 8]. Likewise, the anxiety level appeared to be reasonably low. This is in line with previous reports in such populations of women who opted for prophylactic surgery [5, 13–15]. However, this population appeared to have high endocrine symptom scores and lower sexual functioning. This has also been more or less described in other publications [5, 7, 8, 15, 16].

We showed that a high educational level and occupying an executive position at the time of PBSO positively influenced QOL. In the literature, a history of cancer was the only risk factor reported for a lower QOL [6]. In the present study, a history of breast cancer tended to result in lower physical functioning and social functioning on the QLQ-C30 questionnaire, but this was not statistically significant (p = .04 and p = .06, respectively). This could be explained by the high proportion (77%) of women with a history of cancer in our study. Similarly, a history of mastectomy tended to lead to lower social functioning on the QLQ-C30 questionnaire, but this was not statistically significant (p =.03). We think that this information could be really clinically relevant. Several women spontaneously complained of this condition in the questionnaire because of its psychological impact on their body image.

The women in our series reported fewer endocrine symptoms than those described in previous series [5, 7]. The main difference between our study and those series [5, 7] is the mean interval since PBSO, which were 1.9 years and 2.8 years of follow-up after PBSO, versus 6 years in our study. We assume that such symptoms may be alleviated over time. Finch et al. [17] recently showed that women who were premenopausal at the time of prophylactic oophorectomy experienced significantly higher rates of hot flashes, night sweats, and sweating than menopausal women. Moreover, they reported that premenopausal women with a previous diagnosis of breast cancer had significantly more vasomotor symptoms before surgery than premenopausal unaffected women [17]. In our study, neither the menopausal status before PBSO nor a previous diagnosis of breast cancer influenced endocrine

symptoms (Table 6). However, a young age at surgery tended to have a greater influence on sexual function (p = .001) and endocrine symptoms (p = .003) in our study (Table 6).

Although a high educational level and occupying an executive position were positively associated with QOL, in contrast, a younger age at PBSO was associated with lower social functioning and greater anxiety. Preoperative counseling may therefore be particularly important in young women or women with a low educational level and no occupation. These women should be carefully informed of possible side effects and should receive psychological care before and after PBSO.

In this study, it was not possible to identify women at risk for altered results more accurately, through the construction of a mathematical predictor or a predictive score, because of its retrospective nature and because only a few baseline factors were statistically significant.

The two major results of this study concern the influence of sports practice and weight gain on QOL and overall well-being after PBSO. Practicing a hobby was also a determinant in the univariate analysis but was not significant in the multivariate analysis. Actually, 79% of women practicing a sport also had a hobby. It is impossible to know whether the practice of sport is the cause or a consequence of a good QOL, sexual pleasure, and low anxiety. Regardless, women consulting for PBSO should be aware of this information. Their lifestyle may have an impact on their tolerance of symptoms and their QOL [18].

A prospective comparative study investigated sociodemographic, medical, and psychosocial factors associated with the use of PBSO versus screening among *BRCA1* and *BRCA2* mutation carriers. They found that women with lower or intermediate education levels were more likely to undergo PBSO [19]. In our series, this baseline factor was associated with lower QOL. Women in the PBSO group also had a poorer general health perception, viewed ovarian cancer as an incurable disease, and believed more strongly in the benefits of surgery [19]. Finally, women reported



high levels of satisfaction with their decision to undergo surgery in several studies [7, 20, 21]. This is in accordance with their overall good QOL. Moreover, Madalinska et al. [5] reported lower breast and ovarian cancer anxiety levels in the PBSO group, and 85% of those women said they would choose PBSO again.

CONCLUSION

The main contribution of our work is the identification of patients at potential risk for a more altered well-being after PBSO, such as younger women, women with a low education level, and women without an occupation. We were also able to show that practicing sports, hobbies, and stable weight are associated with better outcomes. These findings open the way for improving the preoperative counseling of

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these women and for constructing pre- and postoperative dedicated intervention programs.

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