Does anti-Müllerian hormone predict change in menopausal symptoms following risk-reducing salpingo-oophorectomy? A prospective observational study

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Objectives

The aim of this study was to investigate whether serum Anti Müllerian hormone (AMH) predict symptom burden after risk-reducing salpingo-oophorectomy (RRSO) in order to individualize counselling.

Methods

Patient-reported menopausal symptoms, sexual functioning and psychological distress (depression and anxiety) were assessed one day before (T0), and six weeks (T1) and seven months (T2) after RRSO. AMH was assessed before RRSO. Multivariable regression analysis was used to investigate the association between AMH and short-term and long-term change in symptom burden following RRSO.

Results

91 premenopausal women at high risk of ovarian cancer were included. Pre-surgical AMH was not related significantly to change in symptoms post-RRSO. As secondary outcome we found that regular menses before RRSO was associated specifically with long-term increase in hot flushes (sr 0.40, p=0.001; total R^2 0.171) and depression (sr 0.29 p=0.012; total R^2 0.132). Earlier receipt of chemotherapy was associated with long-term improvement in sexual functioning (sr 0.24, p=0.041; total R^2 0.348).

Conclusions

In this cohort, AMH was not a significant predictor of change in symptoms following RRSO. Regular menses prior to RRSO and earlier receipt of chemotherapy were significantly, but relatively weakly associated with changes in outcomes six weeks and/or seven months after RRSO.

Keywords: RRSO, AMH, menopause, BRCA1/2, menopausal symptoms, ovarian cancer

Introduction

Approximately 10% of all ovarian carcinomas (OC) are due to inherited predisposition[1]. Ovarian cancer screening is not effective in detecting OC at an earlier stage or in improving prognosis[2]. Therefore, risk-reducing salpingo-oophorectomy (RRSO) is recommended to lower the risk of OC[3]. After RRSO, the risk of OC is reduced by 80%-96%[4, 5, 6]. The recommended age for RRSO after childbearing in BRCA1 carriers is between 35-40 years, and in BRCA2 carriers between 40-45 years. Women from a hereditary breast and ovarian cancer (HBOC) family are advised to undergo RRSO after childbearing is completed, but no specific age is given[4, 6].

A major side-effect of RRSO in premenopausal women is the immediate onset of menopause, accompanied by an increase in non-cancer related morbidity, including a range of endocrine symptoms, sexual symptoms, mood disturbance, as well as an increased risk of cardiovascular disease and osteoporosis[7, 8, 9]. However, there is a wide variability in symptom prevalence and severity, and it is not clear why some women experience more severe symptoms than others. Understanding what factors influence the severity of symptoms following RRSO is important for providing appropriate patient counselling.

To the best of our knowledge, no studies, to date, have investigated predictors of menopausal symptom severity following RRSO. There have been a few studies of predictors of menopausal symptoms in healthy, postmenopausal women. One cross-sectional study found that the severity of menopausal symptoms was significantly influenced by life conditions and events, but not by hormonal changes[10]. Nonetheless, the authors stated that the exact influence of hormones should be investigated in future studies. In another study, these same investigators found that more perceived self-control on hot flushes and night sweats was associated with less severe vasomotor symptoms[11]. A prospective study among

77 women with moderate to severe hot flushes and night sweats reported that negative beliefs
78 about night sweats and sleep were the strongest predictors of concordance between objective
79 and subjective measures of these symptoms[12]. All these studies focused either on lifestyle
80 or psychological variables; none included potential biologic predictors of symptom severity.
81 Previous work has shown that release of anti-Müllerian hormone (AMH) from the
82 granulosa cells of antral follicles leads to measurable serum levels. These concentrations are
83 strongly associated with the number of developing follicles in the ovaries[13]. Because AMH
84 is relatively stable through the menstrual cycle, the measurement of serum AMH has a range
85 of clinical applications, including estimating ovarian reserve and predicting age of natural
86 menopause[14, 15, 16]. A decrease in serum AMH has been found in young women after
87 chemotherapy or anti-hormonal therapy for cancer[17], and it has been suggested that post-
88 chemotherapy AMH levels also predict residual ovarian function[18]. Therefore, AMH is
89 considered to be a marker for the process of ovarian ageing[19]. The 'younger ovary' pattern
90 has higher AMH levels than the 'aging ovary' pattern, suggesting diminishing ovarian reserve
91 as a function of age [20]. Given this background, we hypothesized that the higher the AMH
92 levels pre-RRSO, the more severe the menopausal symptoms post-RRSO.
93 In the present study, we investigated whether higher pre-surgical AMH levels are
94 related to: (1)the severity of post-RRSO menopausal symptoms, in general, and the perceived
95 burden of hot flushes and night sweats, in particular; (2)sexual functioning; and
96 (3)psychological distress (depression and anxiety). In addition to AMH levels, we
97 investigated the possible association between post-RRSO symptoms and a range of
98 sociodemographic and clinical variables. If successful in identifying relevant predictors of
99 symptom severity, this information could be used in counselling pre-treatment symptom
100 experience.
101 **Methods**
102 ***Research setting and study sample***

This prospective, observational, multicenter study was carried out at The Netherlands Cancer Institute and the Leiden University Medical Center in the Netherlands. The institutional review boards of both centers approved the study. Participants were included from November 2006 until April 2012. Patients with a BRCA1/2 mutation or women from a HBOC family with an estimated risk higher than 10% undergoing RRSO, were eligible[21]. Women were invited to participate at the outpatient clinic by the gynecologist when they decided to undergo an RRSO.

Inclusion criteria were being premenopausal at time of RRSO and understanding the Dutch language. Women were excluded from the study if they had cancer at the time of RRSO. Premenopausal status was defined as having one or more menstrual periods over the last twelve months or using (hormonal) contraception. If a woman did not have menstrual periods due to a hysterectomy, we took age as a proxy indicator of menopausal status. Women younger than 51 years were considered premenopausal and women aged 51 years or older were considered postmenopausal. In the Netherlands, most women are postmenopausal by the age of 51 [22].

Women were invited to participate in the study by their gynecologist at the time they decided to undergo a RRSO. A blood sample was obtained within 24 hours before the RRSO was performed. Women were asked to complete questionnaires at three time points: one day before RRSO (T0), and six weeks (T1) and seven months following surgery (T2). All participants provided written informed consent.

Measures

The respondents' age, education, employment status, relationship status, parity, body mass index (BMI), comorbidities, mutation status, regular menses, history of breast cancer, previous breast cancer treatments and current menopausal status were obtained by self-report. Women were asked if they had regular menses during the past 3 months. If they responded negatively to this question, the reason why the menses was irregular was asked. AMH level

was measured in the serum obtained within 24 hours before RRSO with an enzyme-linked immunosorbent assay (ELISA), 2nd generation (Beckmann Coulter, Brea, California USA). Expected values for premenopausal women range from undetectable (<0.10 µg/l) to 10.6 µg/l (2.5%-97.5%).

The Functional Assessment of Cancer-Therapy-Endocrine Symptoms (FACT-ES) was used to assess endocrine symptoms commonly experienced by women after natural, surgically-induced, or medically-induced menopause. The FACT-ES was used in this population before [23, 24] and a validation study showed that the FACT-ES has acceptable validity reliability and is sensitive to clinically significant change [25]. The FACT-ES consists of 18 items that address a range of menopausal symptoms. Occurrence of each symptom in the past four weeks is scored on a 5-point scale, ranging from 'not at all' to 'very much'. Item scores are summed to obtain a total score (range: 0 – 72), with lower values indicating more menopausal symptoms [25].

We also used the Hot Flush Rating Scale (HFRS) to specifically assess the perceived burden of hot flushes and night sweats over the past week. The HFRS problem rating score is the mean of three 1 to 10 numerical scales assessing the extent to which hot flushes and night sweats were problematic, distressing and cause interference in daily life. Higher scores indicate more problematic symptoms [26][25][24].

We assessed sexual functioning with the Sexual Functioning Questionnaire (SFQ). The SFQ consists of 7 domains: desire (6-items); arousal-sensation (4 items); arousal-lubrication (2 items); orgasm (3 items); enjoyment (6 items); pain (3 items); and partner relationship (2 items). Higher scores indicate better sexual functioning[27].

Finally, we employed the Hospital Anxiety and Depression Scale (HADS) to assess psychological distress. The HADS has two 7-item subscales, one for anxiety and one for depression. A score of between 8 and 10 on the total scale represents a subclinical level of

anxiety or depression. The higher the scores the more clinically relevant the anxiety or depression[28].

Statistical Analysis

Scores of the FACT-ES, HFRS, SFQ, the HADS anxiety and the HADS depression, were calculated according to published scoring algorithms. If 50% or fewer of the items were missing from a multi-item scale, the average of the remaining items was used to calculate the scale score. We also examined the pattern of missing questionnaires at the three time points, and whether the characteristics of respondents with missing questionnaires differed from those with no missing questionnaires.

Due to the non-normal distribution of AMH and the substantial number of AMH levels below the limit of detection, we categorized this measure in three groups: (1) less or equal to 0.10 µg/l; (2) more than 0.10 µg/l and less or equal to 1.0 µg/l; and (3) more than 1.0 µg/l.

Continuous data are presented as means and standard deviations (SD); discrete data as counts and percentage. We used Pearson correlations to examine the association between two continuous variables, Student's t-test for dichotomous and continuous data, and one-way analysis of variance for categorical and continuous data.

We used bivariate and multivariable linear regression analysis to investigate potential predictors (pre-surgical AMH levels, age, education, employment status, relationship status, parity, BMI, comorbidities, mutation status, regular menses, history of breast cancer, potential received breast cancer treatments) of changes in: (1) menopausal symptoms, in general, and in hot flushes and night sweats, in particular; (2) sexuality, and (3) psychological distress. Change scores were calculated from baseline to six weeks (T0-T1; short-term) and seven months (T0-T2; long-term) post-RRSO follow-up. We assessed possible multicollinearity by inspecting the models and calculating the variance inflation factor (VIF). In case of a VIF>10, we took into account the importance of the variables and excluded the variable which doesn't

seem essential to the model. Bivariate analyses with $p<0.10$ were conducted to select potential multivariable predictors. Because serum AMH level was the variable of primary interest, we included it in the multivariable model regardless of whether it was significant at the bivariate level.

We considered $p<0.05$ significant in the multivariable analysis. The adjusted R^2 is the proportion of variance in the dependent variable that is explained by the variables included in the model and the total R^2 is the total amount of variance explained by the independent variables in the regression model. The semipartial (sr) correlation is the variance explained in the dependent variable by a single independent variable.

All statistical analyses were carried out using Stata 12 (StataCorp LLC). With power set at 80% and alpha set at 0.05, a sample of 58 subjects is sufficient to conduct a regression analysis with five predictors, assuming that AMH levels account for 11% or more variability and the complete model would account for 21% or more of the variability in the outcomes.

Results

Population

Women were recruited into the study between November 2006 and April 2012. In total, 124 premenopausal women were invited to participate. Of these 124 women, three women ultimately decided not to undergo an RRSO, six transitioned into post-menopause between the invitation and study inclusion, one was diagnosed with OC, four anticipated logistical problems, two did not provide informed consent, and 17 declined without providing a reason.

The background characteristics of the 91women who participated in the study are described in Table 1. The mean (±SD) age of the participants was 43 (±5) years, 87% were in a relationship (married/cohabitating), 71% had advanced level education, and 85% was employed. Eighty-five percent of the women had a proven BRCA 1/2 mutation, and 28% had a history of breast cancer (BC). At the pre-surgical assessment, half of the women reported having a regular menses, i.e. with regular intervals between 3-6 weeks. The other half of the

women had irregular menses or no menses due to various reasons such as hysterectomy, chemotherapy, hormonal anti-conception or the reason was unknown. Thirty-six women (40%) had AMH levels less or equal to 0.10 µg/l, 32 women (35%) had an AMH level that was more than 0.10 µg/l and less or equal to 1.0 µg/l (35%), and 23 women (25%) had an AMH level greater than 1.0 µg/l (25%).

With the exception of the SFQ, patient reported outcome (PRO) assessments were completed by 86 of the 91 women at baseline, 82 women at six weeks, and 79 women at seven months. The SFQ was completed by 84 women at baseline, 81 women at six weeks, and 58 women at seven months. We found no significant differences in baseline sociodemographic and clinical characteristics or in baseline and follow-up patient-reported menopausal, sexual, depression and anxiety symptoms between women who had completed all assessments and those who had missing assessments on one or both of the follow-up assessments (data not shown).

The extended table 2 (see online appendix) shows the results from the bivariate analyses that were conducted to identify potential predictors of change from baseline to follow-up in symptom outcomes. Those variables for which the association with symptom outcomes was significant at the 0.10 level or lower were selected for inclusion in the subsequent multivariable analyses (extended table 3).

Multivariable predictors of symptom outcomes at six weeks and seven months post RRSO

At the multivariable level (Table 3), AMH levels were not associated significantly with any of the symptom outcomes. When examining the multicollinearity in the SFQ model at six weeks, BC and comorbidity were highly correlated (IF= 10.01). Given this multicollinearity, we decided to include BC in the final model, because we were more interested in this outcome as all women in our study were at risk of BC. Having a relationship (sr -0.22, p=0.046) and having regular menses before RRSO (sr-0.27, p=0.015) were associated with a short-term increase in menopausal symptoms (FACT-ES) (total R2 = 0.143). There were no differences

in the FACT-ES scores at baseline or at six-week follow-up between single women and women in a relationship when excluding the items on sexuality (items 7, 8 and 9). No variables were associated significantly with short-term change in the FACT-ES, HFRS, SFQ or HADS.

In the model for change in SFQ at seven months, tamoxifen was the only hormonal therapy which was reported to have been used. For this reason, we excluded tamoxifen use as a potential predictor in the model. Having regular menses pre-surgery was independently associated with a long-term increase in hot flushes (HFRS: sr 0.40, total $R^2 = 0.171$, p=0.001) and in depression (HADS depression: sr 0.29, total $R^2 = 0.132$, p=0.012). Having received chemotherapy (sr 0.24, total $R^2 = 0.348$, p=0.041) for the treatment of BC prior to RRSO was independently associated with a long-term improvement in sexual functioning (SFQ). We explored this latter finding further by examining the differences in the baseline SFQ scores between women who underwent chemotherapy in the past and women who did not. We found that, at baseline, women who had received chemotherapy in the past showed significantly worse sexual functioning (mean= 90, SD= 35) than women who did not (mean= 113, SD= 25, p=0.005). This suggests that there was more room for improvement in sexual functioning in women who had received chemotherapy in the past. None of the variables investigated were independently associated with long-term change in FACT-ES and anxiety as measured by the HADS.

Discussion

This is the first study to investigate prospectively the potential value of AMH in predicting the change in postmenopausal symptoms after RRSO. Because previous studies reported that AMH could be a marker for the process of ovarian ageing [18, 19, 29], we hypothesized that AMH might predict change in menopausal symptoms: the higher the AMH levels pre-RRSO the worse the menopausal symptoms post-RRSO. This proved not to be the case. A systematic review concluded that AMH is the most

promising currently available biomarker for predicting age at natural menopause[30]. However, it does not predict menopausal transition very well at the extremes of the age range (i.e. very young or very old women) since it has wide prediction intervals[30] and the predictive value is less strong with increasing age and becomes less reliable the closer to menopause[31]. Because the mean age in our sample was 43.0 years, which is relatively late in the reproductive age-range, AMH levels could be less reliable. It may be that self-reported regular menses is a better predictor of menopause, and that could be the reason that we did not find any association between the AMH levels and the patients' self-reported symptom levels.

We found that women with regular menses before surgery reported more endocrine symptoms at six weeks after RRSO and more hot flushes and depressive symptoms at seven months after RRSO. Women with irregular menses are more likely to already be in a transition phase to menopause. It has been hypothesized that the immediate onset of menopause after oophorectomy results in more severe complaints in women who still have regular menses pre-RRSO[32]. This is supported by our results in which we found a greater increase in endocrine and depressive symptoms after RRSO in women with regular pre-surgical menses as compared to those women with irregular menses.

Having a relationship was weakly associated with an increase in menopausal symptoms six weeks after RRSO. An explanation could be that some of the items in the FACTES are more focused on sexuality, such that they might be more relevant for married/cohabitating women than single women. And indeed, analyzing the FACT-ES data without the sexual questions did not yield a significant difference in the prevalence of menopausal symptoms between women with a relationship and single women any more. Unexpectedly, we found an improvement in sexual functioning in women who underwent earlier chemotherapy after RRSO. Both chemotherapy and RRSO are known

for their detrimental effect on ovarian function. Therefore, the effect of RRSO could be less severe in this group of women, because the ovarian function was already negatively altered by the BC treatment in the past. This is supported by the observed difference in baseline SFQ scores.

A limitation of our study is the relatively short follow-up, because differences in patient-reported outcomes might continue to change over a longer period of time. Loss to follow-up for some outcomes is a study limitation and the multiple comparisons could lead to the probability of change findings. Also, there is a minor possibility of incorrectly identifying menopausal status due to hysterectomy or use of hormonal contraceptives. In addition, hormonal contraception could decrease AMH levels by 30% [33]. Because these limitations are subject to such a small group of women, we do not think they would change the outcomes. The strengths of our study include its prospective design, the use of validated questionnaires to assess symptoms, and the relatively large sample size for this specific group of women.

In conclusion, our findings indicate that AMH serum levels do not predict changes in endocrine and sexual symptoms or in psychological distress following RRSO in women at increased risk of OC. Having regular menses prior to RRSO and, to a lesser degree, having a relationship were weakly associated with severe menopausal symptoms after surgery. We suggest that further research focusses on individualizing counseling, not with predictive values, but more in communicative tools such as decision aids. In this way, more women know what to expect after RRSO: this may lower the experienced symptoms and enables women to already think about symptom lowering strategies such as hormone replacement therapy.

The authors report no conflicts of interest.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Met opmaak: Nederlands

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Table 1. Demographics of 91 premenopausal women*	
Variables	**N (%)**
Age (Years)	
Mean (SD)	43.0 (4.8)
Relationship status	
Married/cohabitating	79 (87%)
Single/divorced	12 (13%)
Education	
Primary school to middle level high school	26 (29%)
Advanced vocational/ university	65 (71%)
Employment status	
Full-time or part-time job	77 (85%)
Housewife	8 (9%)
Other	6 (7%)
Children	80 (88%)
BMI (kg/m2)	
Mean (SD)	24.2 (3.4)
Comorbidities (%)	31 (34%)
Gene mutation	
Negative	8 (9%)
Unknown	6 (7%)
BRCA1	49 (54%)
BRCA2	28 (31%)
Oral contraceptive	9 (10%)
Regular menses	46 (51%)
History of BC	25 (28%)
Radiotherapy for BC	14 (15%)
Chemotherapy for BC	15 (17%)
Hormonal therapy for BC	3 (3%)
Tamoxifen	4 (4%)
AMH level µg/L	
median (IQR)	0.34 (≤0.10-1.01)
≤0.10 µg/L	36 (40%)
0.10-1.00 µg/L	32 (35%)
≥1.00 µg/L	23 (25%)

Abbreviations: SD standard deviation; BC breast cancer; AMH Anti-Müllerian hormone; IQR inter quartile range.
*Four women younger than 51 years who underwent hysterectomy were identified as premenopausal women

Table 2. Bivariate analysis of factors associated with complaints after 6 weeks (T1) and 7 months (T2)

	Change in FACT-ES				Change in HFRS				Change in SFQ				Change in HADS depression				Change in HADS anxiety			
	6 weeks		7 months		6 weeks		7 months		6 weeks		7 months		6 weeks		7 months		6 weeks		7 months	
Variables		*P* value		*P* value		*P* value		*P* value		*P* value		*P* value		*P* value		*P* value		*P* value		*P* value
AMH level µg/l (≤0.10) (N=36)	-3 ±11	0.804	-3 ±9	0.161	1 ±2	0.643	1 ±2	0.798	-11 ±30	0.202	-9 ±37	0.579	2 ±4	0.301	1 ±3	0.161	0 ±3	0.513	0 ±3	**0.052**
(0.10-1.00) (N=32)	-4 ±10		-5 ±9		1 ±1		1 ±1		-25 ±38		-19 ±34		0 ±2		0 ±1		-1 ±5		-1 ±3	
(≥1.00) (N=23)	-5 ±11		-8 ±9		1 ±2		1 ±1		-29 ±33		-17 ±29		0 ±5		2 ±4		-1 ±4		0 ±3	

Pearson correlation indicated by r; **bold** indicates P<0.10; continuous variables as mean (±standard deviation); discrete variables as number (percentage). Abbreviations: SD standard deviation; BC breast cancer; AMH Anti-Müllerian hormone; SFQ sexual functioning questionnaire; HADS hospital anxiety and depression scale; HFRS hot flush rating scale; FACT-ES functional assessment of cancer therapy – endocrine symptoms

Table 3 Multivariable analysis at six weeks and seven months

Table 3 Complete mulitvariable analysis of factors associated with dependent variables											
Change at 6 weeks	**Regression coefficient (β) (95% CI)**	**Standard error**	***P* value**	**Semipartial correlation**	**Total R^2**	**Change at 7 months**	**Regression coefficient (β) (95% CI)**	**Standard error**	***P* value**	**Semipartial correlation**	**Total R^2**
FACT-ES					0.143	*FACT-ES*					0.148
AMH ≤0.10 µg/L	ref					AMH ≤0.10 µg/L	ref				
AMH 0.10-1.00 µg/L	1 (-4 to 7)	3	0.622	0.05		AMH 0.10-1.00 µg/L	-1 (-5 to 4)	2	0.786	-0.03	
AMH ≥1.00 µg/L	0.4 (-6 to 7)	3	0.885	0.02		AMH ≥1.00 µg/L	-3 (-8 to 2)	3	0.275	-0.12	
HFRS					0.06	*HFRS*					0.171
AMH ≤0.10 µg/L	ref					AMH ≤0.10 µg/L	ref				
AMH 0.10-1.00 µg/L	-0.5 (-1.3 to 0.4)	0.4	0.299	-0.12		AMH 0.10-1.00 µg/L	-0.5 (-1.4 to 0.3)	0.4	0.207	-0.15	
AMH ≥1.00 µg/L	-0.3 (-1.2 to 0.7)	0.5	0.591	-0.06		AMH ≥1.00 µg/L	-0.9 (-1.9 to 0.0)	0.5	0.057	-0.22	
SFQ					0.219	*SFQ*					0.348
AMH ≤0.10 µg/L	ref					AMH ≤0.10 µg/L	ref				
AMH 0.10-1.00 µg/L	-11 (-32 to 10)	10	0.278	-0.14		AMH 0.10-1.00 µg/L	-9 (-29 to 12)	10	0.406	-0.10	
AMH ≥1.00 µg/L	-16 (-42 to 10)	13	0.229	-0.15		AMH ≥1.00 µg/L	-7 (-32 to 18)	12	0.585	-0.06	
HADS Depression					0.078	*HADS Depression*					0.132
AMH ≤0.10 µg/L	ref					AMH ≤0.10 µg/L	ref				
AMH 0.10-1.00 µg/L	-1.4 (-3 to 0.3)	1	0.107	-0.18		AMH 0.10-1.00 µg/L	-1.3 (-3 to 0.2)	1	0.094	-0.19	
AMH ≥1.00 µg/L	-1.1 (-3 to 0.8)	1	0.251	-0.13		AMH ≥1.00 µg/L	0.3 (-1.4 to 2.0)	1	0.730	0.04	
HADS Anxiety					0.092	*HADS Anxiety*					0.080
AMH ≤0.10 µg/L	ref					AMH ≤0.10 µg/L	ref				
AMH 0.10-1.00 µg/L	-0.8 (-3 to 1)	1	0.459	-0.08		AMH 0.10-1.00 µg/L	-1.5 (-3 to 0.1)	1	0.060	-0.22	
AMH ≥1.00 µg/L	-0.4 ('-3 to 2)	1	0.755	-0.04		AMH ≥1.00 µg/L	0.4 (-1.3 to 2.2)	1	0.618	0.06	

Bold indicates statistical significance, $P < 0.05$. CI = Confidence interval, SD = standard deviation, SFQ = sexual functioning questionnaire, HADS = hospital anxiety and depression scale, HFRS = hot flush rating scale, FACT-ES = functional assessment cancer treat ment - endocrine symptoms, AMH = Anti-Müllerian hormone, BC = breast cancer

Supplemental online material

Extended bivariate and multivariable analysis

Table 2. Extended bivariate analysis of factors associated with complaints after 6 weeks (T1) and 7 months (T2)

	Change in FACT-ES				Change in HFRS				Change in SFQ				Change in HADS depression				Change in HADS anxiety			
	6 weeks		7 months		6 weeks		7 months		6 weeks		7 months		6 weeks		7 months		6 weeks		7 months	
Variables		***P* value**		***P* value**		***P* value**		***P* value**		***P* value**		***P* value**		***P* value**		***P* value**		***P* value**		***P* value**
Age (yrs)	r 0.05	0.676	r 0.02	0.834	r 0.07	0.548	r 0.13	0.271	r -0.13	0.324	r -0.22	**0.094**	r 0.08	0.516	r 0.11	0.347	r -0.03	0.803	r -0.12	0.289
Marital status																				
Married/living together	-4.7 ±10	0.100	-6.0 ±9	**0.096**	0.9 ±2	0.783	1.1 ±2	0.813	-18 ±34	0.306	-12 ±32	**0.046**	0.7 ±3	**0.076**	1.0 ±3	0.741	-0.25 ±4	**0.070**	-0.3 ±3	0.261
Single/divorced	0.6 ±12		-1.1 ±10		1.1 ±1		1.2 ±1		-35 ±36		-43 ±40		-1.3 ±6		1.2 ±4		-2 ±3		-1.4 ±3	
Education																				
Primary school to middle level high school	-4.0 ±7	0.945	-5.8 ±6	0.716	1.2 ±1	0.448	1.1 ±1	0.913	-31 ±34	**0.096**	-21 ±25	0.414	0.3 ±2	0.776	0.6 ±2	0.458	-0.7 ±5	0.826	-0.5 ±3	0.899
Advanced vocational/ university	-3.8 ±11		5.0 ±10		0.8 ±2		1.1 ±2		-15 ±33		-12 ±37		0.5 ±4		1.2 ±3		-0.5 ±3		-0.4 ±3	
Employment																				
Full-time or part-time job	-4.3 ±9	**0.040**	-5.1 ±9	0.641	1.0 ±2	0.069	1.1 ±2	0.629	-21 ±34	0.820	-17 ±33	**0.070**	0.4 ±3	0.751	0.9 ±3	0.636	-0.5 ±4	0.783	-0.4 ±3	0.736
Housewife	-5.6 ±6		-7.6 ±5		1.6 ±2		0.9 ±1		-11 ±16		-24 ±18		0.6 ±3		0.0 ±1		-1.3 ±4		-1.2 ±2	
Other	6.4 ±17		-2.2 ±10		-0.5 ±1		0.2 ±0		-13 ±54		23 ±49		-0.7 ±7		1.8 ±2		-1.5 ±4		-1.3 ±2	
Children																				
0	-4.4 ±8	0.854	-3.6 ±8	0.531	0.7 ±1	0.602	0.9 ±1	0.701	-30 ±31	0.435	-14 ±17	0.959	-0.9 ±3	0.224	0.1 ±2	0.304	-1.7 ±4	0.370	-0.1 ±2	0.706
1 or more	-3.8 ±11		-5.5 ±9		1.0 ±2		1.1 ±2		-18 ±35		-15 ±35		0.6 ±3		1.1 ±3		-0.4 ±4		-0.5 ±3	
BMI (kg/m²)	r 0.01	0.961	r 0.11	0.359	r 0.06	0.620	r -0.03	0.809	r -0.02	0.891	r -0.04	0.760	r -0.08	0.480	r -0.166	0.154	r 0.02	0.869	r -0.08	0.483
Comorbidities																				
yes	-4.5 ±9	0.415	-3.6 ±10	0.289	0.9 ±2	0.814	1.3 ±2	0.458	-4 ±27	**0.007**	-20 ±27	0.107	0.5 ±3	0.823	1 ±3	0.979	0.2 ±4	0.167	-0.1 ±3	0.579
no	-2.5 ±12		-6.0 ±9		1.0 ±1		1.0 ±1		-28 ±35		-5 ±43		0.3 ±5		1 ±3		-1 ±4		-0.6 ±3	
Gene mutation																				
Negative	-6.7 ±14	0.854	-7.5 ±12	0.870	1.9 ±2	0.357	1.4 ±1	0.913	-13 ±14	0.130	-5 ±15	0.722	1.8 ±2	0.713	0.7 ±1	0.319	0.5 ±2	0.838	0.3 ±2	0.549
Unknown	-2.5 ±7		-6.7 ±6		0.8 ±1		1.1 ±1		-92 ±0		-39 ±10		-0.4 ±2		0 ±1		1 ±4		-0.3 ±3	
BRCA1	-3.2 ±11		-4.6 ±8		1.0 ±2		1.1 ±2		-16 ±33		-14 ±40		0.4 ±4		0.6 ±2		-0.8 ±4		-0.9 ±3	

BRCA2	-4.5 ±9		-5.4 ±11		0.6 ±1		0.9 ±2		-25 ±36		-16 ±27		0.2 ±3		1.9 ±4		-0.4 ±4		0.1 ±3	
Oral contraceptive before surgery																				
yes	-4.5 ±15	0.858	-2.8 ±10	0.389	1.0 ±2	0.982	1.0 ±2	0.819	-17 ±34	0.842	-4 ±23	0.418	0 ±6	0.738	0.4 ±2	0.555	-0.7 ±4	0.930	0 ±2	0.643
no	-3.8 ±10		-5.6 ±9		0.9 ±2		1.0 ±1		-20 ±34		-16 ±35		0.5 ±3		1.1 ±3		-0.6 ±4		-0.5 ±3	
Regular menses																				
yes	-6.2 ±12	**0.031**	-7.3 ±10	**0.031**	1.2 ±1	0.172	1.6 ±1	**0.004**	-26 ±33	0.192	-20 ±31	0.167	1 ±4	0.118	1.7 ±4	**0.018**	-0.3 ±4	0.507	-0.2 ±3	0.540
no	-1.2 ±7		-2.9 ±7		0.7 ±2		0.5 ±1		-14 ±34		-8 ±36		-0.2 ±2		0.2 ±2		-0.9 ±4		-0.7 ±3	
History of Breast cancer																				
yes	-3.0 ±10	0.657	-3.3 ±10	0.285	0.8 ±2	0.600	1.0 ±2	0.823	-3 ±29	**0.009**	-6 ±47	0.223	0.5 ±3	0.892	0.8 ±3	0.800	0.5 ±3	**0.096**	-0.2 ±4	0.688
no	-4.2 ±11		-5.9 ±9		1 ±2		1.1 ±2		-27 ±34		-18 ±27		0.4 ±4		1.0 ±3		-1.1 ±3		-0.5 ±3	
Radiotherapy for breast cancer																				
yes	-1.5 ±11	0.360	-5.9 ±9	0.112	0.5 ±2	0.287	0.5 ±2	0.175	2 ±36	**0.017**	1 ±63	0.120	-0.2 ±2	0.512	1.2 ±4	0.805	-0.9 ±4	0.182	0.7 ±3	0.237
no	-4.3 ±10		-1.1 ±10		1 ±2		1.2 ±2		-25 ±32		-18 ±25		0.5 ±4		1.0 ±3		0.7 ±3		-0.6 ±3	
Chemotherapy for breast cancer																				
yes	-1.8 ±11	0.407	-1.9 ±11	0.156	0.4 ±2	0.157	0.8 ±2	0.423	-0,4 ±35	**0.019**	13 ±42	**0.002**	0.1 ±3	0.679	-0.3 ±2	0.109	-0.9 ±4	0.180	-0.3 ±3	0.567
no	-4.3 ±10		-5.9 ±8		1.1 ±2		1.1 ±2		-25 ±32		-21 ±29		0.5 ±3		1.2 ±3		0.6 ±3		-0.9 ±4	
Hormonal therapy for breast cancer																				
yes	2.7 ±8	0.263	3.5 ±10	**0.083**	-0.3 ±1	0.149	-0.2 ±2	0.132	23 ±35	**0.022**	35 ±51	**0.008**	-1.7 ±3	0.283	-0.7 ±5	0.319	0 ±3	0.785	-1.3 ±3	0.594
no	-4.1 ±10		-5.6 ±9		1.0 ±2		1.1 ±1		-22 ±33		-17 ±31		0.5 ±3		1.1 ±3		-0.6 ±4		-0.4 ±3	
Tamoxifen																				
yes	1.5 ±7	0.288	3.5 ±10	**0.083**	-0.3 ±1	0.116	-0.2 ±2	0.132	16 ±32	**0.030**	35 ±51	**0.008**	-1 ±3	0.397	-0.7 ±5	0.319	-0.5 ±3	0.961	-1.3 ±3	0.594
no	-4.1 ±10		-5.6 ±9		1 ±2		1.1 ±1		-22 ±33		-17 ±31		0.5 ±3		1.1 ±3		-0.6 ±4		-0.4 ±3	
AMH level µg/l																				
(≤0.10) (N=36)	-3 ±11	0.804	-3 ±9	0.161	1 ±2	0.643	1 ±2	0.798	-11 ±30	0.202	-9 ±37	0.579	2 ±4	0.301	1 ±3	0.161	0 ±3	0.513	0 ±3	**0.052**
(0.10-1.00) (N=32)	-4 ±10		-5 ±9		1 ±1		1 ±1		-25 ±38		-19 ±34		0 ±2		0 ±1		-1 ±5		-1 ±3	
(≥1.00) (N=23)	-5 ±11		-8 ±9		1 ±2		1 ±1		-29 ±33		-17 ±29		0 ±5		2 ±4		-1 ±4		0 ±3	

Pearson correlation indicated by r; **bold** indicates P<0.10; continuous variables as mean (±standard deviation); discrete variables as number (percentage). Abbreviations: SD

standard deviation; BC breast cancer; AMH Anti-Müllerian hormone; SFQ sexual functioning questionnaire; HADS hospital anxiety and depression scale; HFRS hot flush rating scale; FACT-ES functional assessment of cancer therapy – endocrine symptoms

Table 3 Complete mulitvariable analysis of factors associated with dependent variables

Change at 6 weeks	**Regression coefficient (β) (95% CI)**	**Standard error**	***P* value**	**Semipartial correlation**	**Total R^2**
FACT-ES					0.143
Stable relationship (married/cohabitating)	-6 (-13 to -0.1)	3	**0.046**	-0.22	
Employment					
Other	ref				
Working	-6 (-13 to 2)	4	0.122	-0.17	
Housewife	-8 (-19 to 3)	6	0.175	-0.15	
Regular menses (yes vs no)	-6 (-11 to -1.2)	2	**0.015**	-0.27	
AMH ≤0.10 µg/L	ref				
AMH 0.10-1.00 µg/L	1 (-4 to 7)	3	0.622	0.05	
AMH ≥1.00 µg/L	0.4 (-6 to 7)	3	0.885	0.02	
HFRS					0.06
Employment					
Other	ref				
Working	1,0 (-0.2 to 2.1)	1	0.111	0.19	
Housewife	1.5 (-0.3 to 3.2)	1	0.104	0.20	
AMH ≤0.10 µg/L	ref				
AMH 0.10-1.00 µg/L	-0.5 (-1.3 to 0.4)	0.4	0.299	-0.12	
AMH ≥1.00 µg/L	-0.3 (-1.2 to 0.7)	0.5	0.591	-0.06	

Change at 7 months	**Regression coefficient (β) (95% CI)**	**Standard error**	***P* value**	**Semipartial correlation**	**Total R^2**
FACT-ES					0.148
Stable relationship (married/cohabitating)	-5 (-11 to 0.3)	3	0.062	-0.21	
Regular mensis (yes vs no)	-4 (-8 to 0.6)	2	0.089	-0.19	
Hormonal therapy for BC (yes vs no)	7 (-3 to 17)	5	0.175	0.15	
AMH ≤0.10 µg/L	ref				
AMH 0.10-1.00 µg/L	-1 (-5 to 4)	2	0.786	-0.03	
AMH ≥1.00 µg/L	-3 (-8 to 2)	3	0.275	-0.12	
HFRS					0.171
Regular mensis (yes vs no)	1.3 (0.6 to 2.1)	0.4	**0.001**	0.09	
AMH ≤0.10 µg/L	ref				
AMH 0.10-1.00 µg/L	-0.5 (-1.4 to 0.3)	0.4	0.207	-0.15	
AMH ≥1.00 µg/L	-0.9 (-1.9 to 0.0)	0.5	0.057	-0.22	

SFQ					0.219
Education	18 (-3 to 39)	10	0.088	0.21	
History of BC (yes vs no)	4 (-31 to 39)	18	0.818	0.03	
Radiotherapy for BC (yes vs no)	4 (-30 to 37)	17	0.834	0.03	
Chemotherapy for BC (yes vs no)	4 (-32 to 41)	18	0.817	0.03	
Hormonal therapy for BC (yes vs no)	7 (-75 to 88)	41	0.870	0.02	
Tamoxifen (yes vs no)	29 (-47 to 105)	38	0.441	0.10	
AMH ≤0.10 µg/L	ref				
AMH 0.10-1.00 µg/L	-11 (-32 to 10)	10	0.278	-0.14	
AMH ≥1.00 µg/L	-16 (-42 to 10)	13	0.229	-0.15	
HADS Depression					0.078
Stable relationship (married/cohabitating)	2.1 (-0.1 to 4.3)	1	0.060	0.22	
AMH ≤0.10 µg/L	ref				
AMH 0.10-1.00 µg/L	-1.4 (-3 to 0.3)	1	0.107	-0.18	
AMH ≥1.00 µg/L	-1.1 (-3 to 0.8)	1	0.251	-0.13	
HADS Anxiety					0.092
Stable relationship (married/cohabitating)	2.3 (-0.06 to 4.6)	1	0.056	0.22	
History of BC (yes vs no)	1.5 (-0.5 to 3.5)	1	0.148	0.17	
AMH ≤0.10 µg/L	ref				

SFQ					0.348
Age (years)	-1 (-2.9 to 0.8)	0.9	0.269	-0.13	
Stable relationship (married/cohabitating)	25 (-4 to 54)	15	0.094	0.20	
Employment					
Other	ref				
Working	-19 (-44 to 6)	13	0.137	-0.17	
Housewife	-28 (-66 to 9)	19	0.133	-0.18	
Chemotherapy for BC (yes vs no)	23 (1 to 45)	11	**0.041**	0.24	
Hormonal therapy for BC (yes vs no)	36 ('-1 to 74)	19	0.057	0.22	
AMH ≤0.10 µg/L	ref				
AMH 0.10-1.00 µg/L	-9 (-29 to 12)	10	0.406	-0.10	
AMH ≥1.00 µg/L	-7 (-32 to 18)	12	0.585	-0.06	
HADS Depression					0.132
Regular menses (yes vs no)	1.7 (0.4 to 3.1)	0.7	**0.012**	0.29	
AMH ≤0.10 µg/L	ref				
AMH 0.10-1.00 µg/L	-1.3 (-3 to 0.2)	1	0.094	-0.19	
AMH ≥1.00 µg/L	0.3 (-1.4 to 2.0)	1	0.730	0.04	
HADS Anxiety					0.080
AMH ≤0.10 µg/L	ref				

AMH 0.10-1.00 µg/L	-0.8 (-3 to 1)	1	0.459	-0.08	AMH 0.10-1.00 µg/L	-1.5 (-3 to 0.1)	1	0.060	-0.22
AMH ≥1.00 µg/L	-0.4 ('-3 to 2)	1	0.755	-0.04	AMH ≥1.00 µg/L	0.4 (-1.3 to 2.2)	1	0.618	0.06

Bold indicates statistical significance, $P < 0.05$. CI = Confidence interval, SD = standard deviation, SFQ = sexual functioning questionnaire, HADS = hospital anxiety and depression scale, HFRS = hot flush rating scale, FACT-ES = functional assessment cancer treatment - endocrine symptoms, AMH = Anti-Müllerian hormone, BC = breast cancer