



Treatment-induced symptoms, depression and age as predictors of sexual problems in premenopausal women with early breast cancer receiving adjuvant endocrine therapy

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Abstract

Purpose Sexual dysfunction is an important concern of premenopausal women with early breast cancer. We investigated predictors of sexual problems in two randomized controlled trials.

Methods A subset of patients enrolled in TEXT and SOFT completed global and symptom-specific quality-of-life indicators, CES-Depression and MOS-Sexual Problems measures at baseline, six, 12 and 24 months. Mixed models tested the association of changes in treatment-induced symptoms (baseline to 6 months), depression at 6 months, and age at randomization with changes in sexual problems over 2 years.

Results Sexual problems increased by 6 months and persisted at this level. Overall, patients with more severe worsening of vaginal dryness, sleep disturbances and bone or joint pain at 6 months reported a greater increase in sexual problems at all time-points. Depression scores were significantly associated with sexual problems in the short-term. All other symptoms had a smaller impact on sexual problems. Age was not associated with sexual problems at any time-point.

Conclusion Among several key symptoms, vaginal dryness, sleep disturbance, and bone and joint pain significantly predicted sexual problems during the first 2 years. Early identification of these symptoms may contribute to timely and tailored interventions.

Keywords Sexual problems · Breast cancer · Endocrine treatment · Treatment-induced symptoms · Depression

Introduction

Sexual dysfunction has been identified as one of the most common and distressing consequences of cancer treatment [1, 2]. In women with breast cancer, reported prevalence of sexual dysfunction varies widely [1, 3–7] depending on study design, type and time-point of assessment, menopausal status and treatment received. In women with prior breast cancer, there is greater prevalence and persistence of sexual problems than in healthy controls [3, 8–11].

In women who are still premenopausal, any cancer treatment that causes abrupt, premature ovarian failure increases the risk of sexual dysfunction [12]. In young women who experienced early menopause from treatment, sexual dysfunction was worse compared to those who continued menstruation [3, 13]. Randomized controlled trials in premenopausal women with breast cancer receiving oral adjuvant

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Trial Registration: clinicaltrials.gov NCT00066703 (TEXT) and NCT00066690 (SOFT).

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endocrine treatment with or without ovarian function suppression (OFS) reported a worsening in sexual functioning over time [14–17]. The focus of prior analyses in these trials was on treatment differences without investigating predictors of sexual dysfunction.

A variety of predictors of sexual functioning have been studied, most of them in mixed populations of pre- and postmenopausal women with breast cancer and with data obtained from cross-sectional designs, which do not allow inference regarding causal relationships. Data from longitudinal observational studies are less frequently reported [18, 19]. Some studies reported no associations between different treatment modalities and sexual dysfunction, [20–23], while others found that mastectomy, [3, 6, 10, 24] chemotherapy [13, 18, 19, 25] or endocrine therapy [26–30] had a negative impact on sexual functioning. Sexual dysfunction has also been associated with menopausal symptoms [18, 24, 26, 31], nausea [21], insomnia [21], fatigue [13], weight gain [6], body mass index [32, 33], depressive symptoms [9, 18, 19, 28] and anxiety [34]. Poorer sexual functioning has been reported by patients between 40 and 60 years of age compared to younger or older cohorts [8, 20, 35].

We investigated predictors of changes in sexual problems over the first 24 months of adjuvant endocrine therapy, in premenopausal women with hormone receptor-positive early breast cancer who were enrolled in the TEXT (Tamoxifen and Exemestane Trial) or SOFT (Suppression of Ovarian Function Trial) trials coordinated by the International Breast Cancer Study Group (IBCSG) [36, 37].

Patients and methods

Participants

The sample for this analysis comprised patients participating in TEXT or SOFT from centers with English as primary language (i.e., centers located in Australia, Canada, Ireland, New Zealand, South Africa, United Kingdom and United States) who completed supplemental questionnaires assessing sexual problems and depression (Fig. 1).

The TEXT randomized phase III trial was designed to investigate the question of 5 years treatment with the aromatase inhibitor (AI) exemestane (E) compared to tamoxifen (T) in patients who received OFS from the start of adjuvant therapy [36]. SOFT is a three-arm, randomized phase III trial designed to investigate the role of OFS and the role of exemestane in patients who remained premenopausal after completion of (neo)adjuvant chemotherapy and in patients for whom adjuvant tamoxifen alone (without chemotherapy) was considered suitable treatment [37].

Eligibility criteria for TEXT and SOFT criteria have been described [36, 37]. Details on adjuvant treatment administration are provided in the supplementary material. Ethics committees and appropriate national health authorities from each center (see list in supplementary material) approved the protocol, and all patients provided written informed consent.

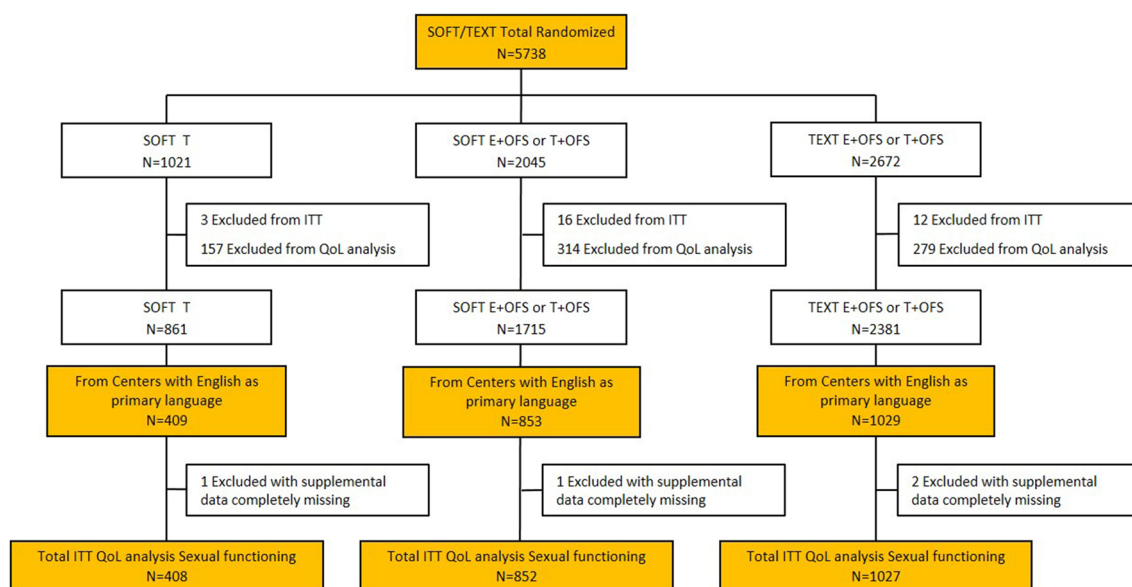


Fig. 1 CONSORT Flow chart for patients randomized in SOFT and TEXT included in the sexual problems analysis. *TEXT* Tamoxifen and Exemestane Trial, *SOFT* Suppression of Ovarian Function Trial,

OFS ovarian function suppression, *E* exemestane, *T* tamoxifen, *QoL* quality-of-life, *ITT* intention-to-treat

Measures

Sexual problems were measured by the Medical Outcome Study-Sexual Problems scale (MOS-SP) [38], which consists of 4 items covering the dimensions sexual interest, arousal and orgasm as defined by internationally accepted diagnostic criteria (DSM-5/ICD-10). Its psychometric properties are acceptable [39], and although not specifically validated in patients with breast cancer, it has been used in this setting [31, 40]. Responses options are (1) not a problem, (2) little of a problem, (3) somewhat of a problem; (4) very much a problem, and the option to respond with “not applicable”. Each item was analyzed individually (score range 1–4). In addition, the MOS-SP total score (sum of individual items; range 4–16) was rescaled from 0 to 100 with higher scores indicating more severe sexual problems. The MOS-SP was designed to be applicable for persons without a partner or who had not had sexual experience during the period of interest [38]. Previous validation of the MOS-SP suggested that persons in this situation responded with “not a problem” rather than “not applicable” to the questions. It is recommend to recode “not applicable” responses as “not a problem” [38]. A cross-checking of two MOS-SP items (lack of sexual interest; difficulties becoming aroused) with corresponding LASA items (score range 0–100) on the trial-specific module [15, 17] and checking a sample of individual patients’ records of this analysis support this decision (data not shown).

In the absence of established criteria for a minimal clinically important difference for the MOS-SP total score, we defined a change of at least ± 8 points as clinically meaningful, according to a distribution-based method suggested for the interpretation of QoL endpoints in clinical trials [41]. An ad hoc item assessing pain or discomfort with intercourse in the same response format was added to the four items but handled as single-item [15, 17, 38].

Symptoms related to endocrine therapy were assessed by selected symptom-specific QoL indicators from the English version of the IBCSG QoL Core Form [42] and a trial-specific module [15, 17]. All indicators were single-items in linear analogue self-assessment (LASA) format, transformed to range from 0–100 with higher numbers reflecting a better condition [43]. Adjuvant breast cancer trials that examined the impact of chemotherapy and endocrine therapy confirmed the clinical relevance of specific LASA indicators [15, 17, 44]. A clinically meaningful change was defined as at least ± 8 points [41].

Depression was measured by the Center of Epidemiologic Studies-Depression Scale (CES-D), [45] a 20-item self-report measure for depressive symptomatology during the previous week. It is one of the most efficient screening measures for depression in cancer patients [46]. Scores range from 0 to 60 with higher summary scores indicating

more severe depressive symptoms. Scores are summarized as continuous measures categorized in three distinct groups: No evidence of clinical depression (score < 15), evidence of mild to moderate (15–21), and of major depression (22–60).

Cohorts

The SOFT/TEXT patient-reported outcome primary analyses confirmed that chemotherapy use and timing relative to trial baseline are important variables in the interpretation of symptom reporting [15, 17]. Based on the intention-to-treat approach, we considered the following five cohorts of patients according to chemotherapy use, trial and treatment assignment:

- Cohort 1: tamoxifen alone (no chemo SOFT T);
- Cohort 2: prior chemotherapy followed by tamoxifen alone (prior chemo SOFT T)
- Cohort 3: prior chemotherapy followed by oral endocrine therapy plus OFS (prior chemo SOFT E + OFS, T + OFS);
- Cohort 4: oral endocrine therapy plus OFS (no chemo SOFT/TEXT E + OFS, T + OFS);
- Cohort 5: chemotherapy concurrently with OFS before initiating oral endocrine therapy (chemo TEXT E + OFS, T + OFS)

Hypotheses

We prospectively defined following hypotheses:

- 1 Women who report more severe changes in key symptoms during the first 6 months of therapy will report greater worsening of sexual problems at the follow-up time-points (primary endpoint: 24 months).
- 2 Women who report scores likely to indicate depression at 6 months will report a greater worsening in sexual problems at 24 months.
- 3 Younger premenopausal women will report greater worsening of sexual problems at six, 12, and 24 months than older premenopausal women.

Analyses

Patients were excluded from all TEXT/SOFT QoL analyses if they (1) suffered from cognitive or physical impairment that interfered with the QoL assessment; (2) were from participating centers with poor overall QoL submission rates (< 60% of QoL assessments completed between baseline and 24 months); (3) had otherwise no QoL data submitted (Fig. 1) [15, 17].

Analyses were performed according to the five cohorts and overall. We selected the following key endocrine

symptoms as potential predictors for sexual problems based on previous studies [6, 11, 13, 18, 21, 24, 26, 31]: hot flushes, vaginal dryness, sleep disturbance, troubled by weight gain, and bone or joint pain. The two symptoms tiredness and feeling sick (nausea and/or vomiting) were added to the analysis in order to take into account side effects of chemotherapy.

For testing hypothesis one, median changes from baseline to 6 months for each symptom indicator were used to define more and less severe changes of symptoms. For hypothesis two, depression status was defined by dichotomizing CES-D summary score at 6 months as no depression (< 15) vs. depression (≥ 15). We also controlled for the use of anti-depressants at completion of 6-month MOS-SP (yes vs no). We matched the start and end date of anti-depressants use (antiD) with the 6-month QoL completion date (include if antiD start date is > 10 days from QoL completion date; exclude if antiD end date > 30 days prior to QoL completion date). For testing hypothesis 3, age groups were defined as < 40 and ≥ 40 years.

The outcome was the change in sexual problems over time relative to baseline, and the MOS-SP score was re-defined as the change from baseline to each time-point so that a positive value represents an increase in sexual problems. Patients with missing baseline values did not contribute to these analyses. All available data were analyzed without imputation of missing data.

Mixed-effects linear modeling for repeated measures analyzed the associations of key symptoms, depression status and age with changes in sexual problems over 2 years. The model included severity groups of the seven key symptoms, depression status, age, baseline covariates, five cohorts, treatment assignment, time-points (6, 12, 24 months), and interactions of symptoms, time-points and cohorts. Age groups (< 35 , 35–39, 40–44, 45–49, 50+) were used except for testing hypothesis 3. Baseline covariates included race, BMI performance status, menstruation status, type of surgery, family history of breast cancer, nodal status, tumor size, tumor grade, and HER2 status (Table 1). An unstructured covariance was used. Within each cohort and overall, model contrasts estimated differences between symptom severity groups, 95% confidence intervals (CI), and tested whether the difference deviated from zero, at six, 12 and 24 months.

Although the hypotheses were stated as one-sided, tests were two-sided. The reported P-values were not adjusted for multiple testing in order to look for consistency of the signal among similar QoL indicators. At the time of analysis, the median follow-up was 5.7 years [15].

Results

Patient and disease characteristics

A total of 2287 of 5738 patients enrolled in TEXT and SOFT were analyzed (1260 in SOFT, 1027 in TEXT). Overall, the median age was 43 years (Table 1). Patients from the two cohorts who received no chemotherapy were older (median 46 years) than those from the cohorts with prior or concurrent chemotherapy (median age 39 to 43 years). About 30% of patients in the cohorts with prior chemotherapy had persistent amenorrhea compared to less than 10% in the other three cohorts. Overall, 46% of patients had a mastectomy, 54% breast-conserving surgery, which varied among cohorts. Approximately 40% of patients in the cohorts with prior chemotherapy had taken tamoxifen before enrollment. QoL forms submission rates were 99% at baseline, 89% at 6 months, 85% at 12 months, and 81% at 24 months.

Sexual problems over time

Baseline scores for the MOS-SP total score were worse for the two cohorts with prior chemotherapy compared to the other three cohorts (Table S1). Overall, the proportion of women who reported more than minor problems in the MOS-SP domains were between 20 and 30% at baseline and increased approximately another 10% up to 24 months (Table 2, Table S2).

Across cohorts, the MOS-SP total score worsened clinically meaningfully over time (Fig. 2, Table S3). Patients in the two cohorts assigned either T + OFS or E + OFS reported the most pronounced worsening in the MOS-SP total score, irrespective of whether they had concurrent or no chemotherapy. Women assigned T-alone, with or without prior chemotherapy, were the least affected by sexual problems during the whole observation period (Fig. 2, Table S3). MOS-SP individual items and the ad hoc item for pain or discomfort with intercourse worsened during the first 6 months and remained thereafter on the same level up to 24 months (Fig. 2).

Predictors of sexual problems

All key symptoms (except feeling sick) significantly predicted sexual problems in the short-term (at 6 months, Table 3). Among these symptoms, a more severe worsening of vaginal dryness, sleep disturbance, and bone or joint pain in the short-term was associated with a greater worsening of sexual problems up to 24 months in the overall population (hypothesis 1, Table 3).

Table 1 Characteristics of patients overall and according to chemotherapy cohort and treatment assignment

	No Chemo SOFT T		Prior Chemo SOFT T		Prior Chemo SOFT E + OFS, T + OFS		No Chemo SOFT/TEXT E + OFS, T + OFS		Chemo TEXT E + OFS, T + OFS		Overall	
	N	%	N	%	N	%	N	%	N	%	N	%
Total	156	100.0	252	100.0	524	100.0	684	100.0	671	100.0	2287	100.0
Age, years												
< 35	1	0.6	51	20.2	119	22.7	16	2.3	72	10.7	259	11.3
35–39	12	7.7	77	30.6	125	23.9	40	5.8	114	17.0	368	16.1
40–44	40	25.6	77	30.6	174	33.2	197	28.8	229	34.1	717	31.4
45–49	75	48.1	37	14.7	87	16.6	294	43.0	221	32.9	714	31.2
50+	28	17.9	10	4.0	19	3.6	137	20.0	35	5.2	229	10.0
Median [IQR]	46	[43, 49]	39	[35, 43]	40	[35, 44]	46	[43, 49]	43	[39, 46]	43	[47, 58]
Race												
White/Caucasian	139	89.1	209	82.9	432	82.4	603	88.2	569	84.8	1952	85.4
Other	17	10.8	40	15.9	83	15.8	77	11.3	95	14	312	13.6
Unknown	–	–	3	1.2	9	1.7	–	–	3	1.2	23	0.1
BMI												
Median [IQR]	26	[23, 32]	27	[23, 33]	27	[24, 32]	25	[22, 30]	26	[23, 31]	26	[23, 31]
Menstruation status												
Normal	116	74.4	91	36.1	199	38.0	515	75.3	557	83.0	946	41.4
Irregular	27	17.3	81	32.1	160	30.5	124	18.1	61	9.1	625	27.3
Persistent amenorrhea	12	7.7	74	29.4	153	29.2	36	5.3	42	6.3	693	30.3
Unknown	1	0.6	6	2.4	12	2.3	9	1.3	11	1.6	23	1.0
Family history												
No	84	53.8	148	58.7	268	51.1	354	51.8	369	55.0	1223	53.5
Yes	71	45.5	101	40.1	247	47.1	324	47.4	289	43.1	1032	45.1
Adopted	1	0.6	3	1.2	7	1.3	6	0.9	13	1.9	30	1.3
Unknown	–	–	–	–	2	0.4	–	–	–	–	2	0.1
Performance status												
Fully active (K90–100)	148	94.9	230	91.3	471	89.9	649	94.9	634	94.5	2132	93.2
Restricted (K70–80)	8	5.1	19	7.5	48	9.2	31	4.5	33	4.9	139	6.1
Ambulatory, no work (K50–60)	–	–	1	0.4	–	–	–	–	2	0.3	3	0.1
Unknown	–	–	2	0.8	5	1.0	4	0.6	2	0.3	13	0.6
Nodal status												
Negative	144	92.3	111	44.0	226	43.1	625	91.4	271	40.4	1377	60.2
Positive	11	7.1	140	55.6	297	56.7	53	7.7	398	59.3	899	39.3
Tumor size > 2 cm	17	10.9	108	42.9	244	46.6	99	14.5	326	48.6	794	34.7
Tumor grade												
1	77	49.4	35	13.9	66	12.6	276	40.4	114	17.0	568	24.8
2	65	41.7	114	45.2	268	51.1	356	52.0	314	46.8	1117	48.8
3	12	7.7	98	38.9	186	35.5	43	6.3	240	35.8	579	25.3
Unknown	2	1.3	5	2.0	4	0.8	9	1.3	3	0.4	23	1.0
HER2-positive	16	10.3	49	19.4	132	25.2	40	5.8	119	17.7	356	15.6
Local therapy												
Mastectomy	55	35.3	135	53.6	304	58.0	235	34.3	331	49.4	1060	46.3
Breast conserving surgery	101	64.8	117	46.4	220	42.0	449	65.7	340	50.6	1227	53.7
Endocrine therapy before randomization	11	7.1	104	41.3	212	40.5	25	3.7	–	–	352	15.4
Prior endocrine therapy duration Median weeks, [IQR]	6	[3, 8]	18	[10, 23]	16	[10, 22]	4	[2, 8]	–	–	15	[8, 22]

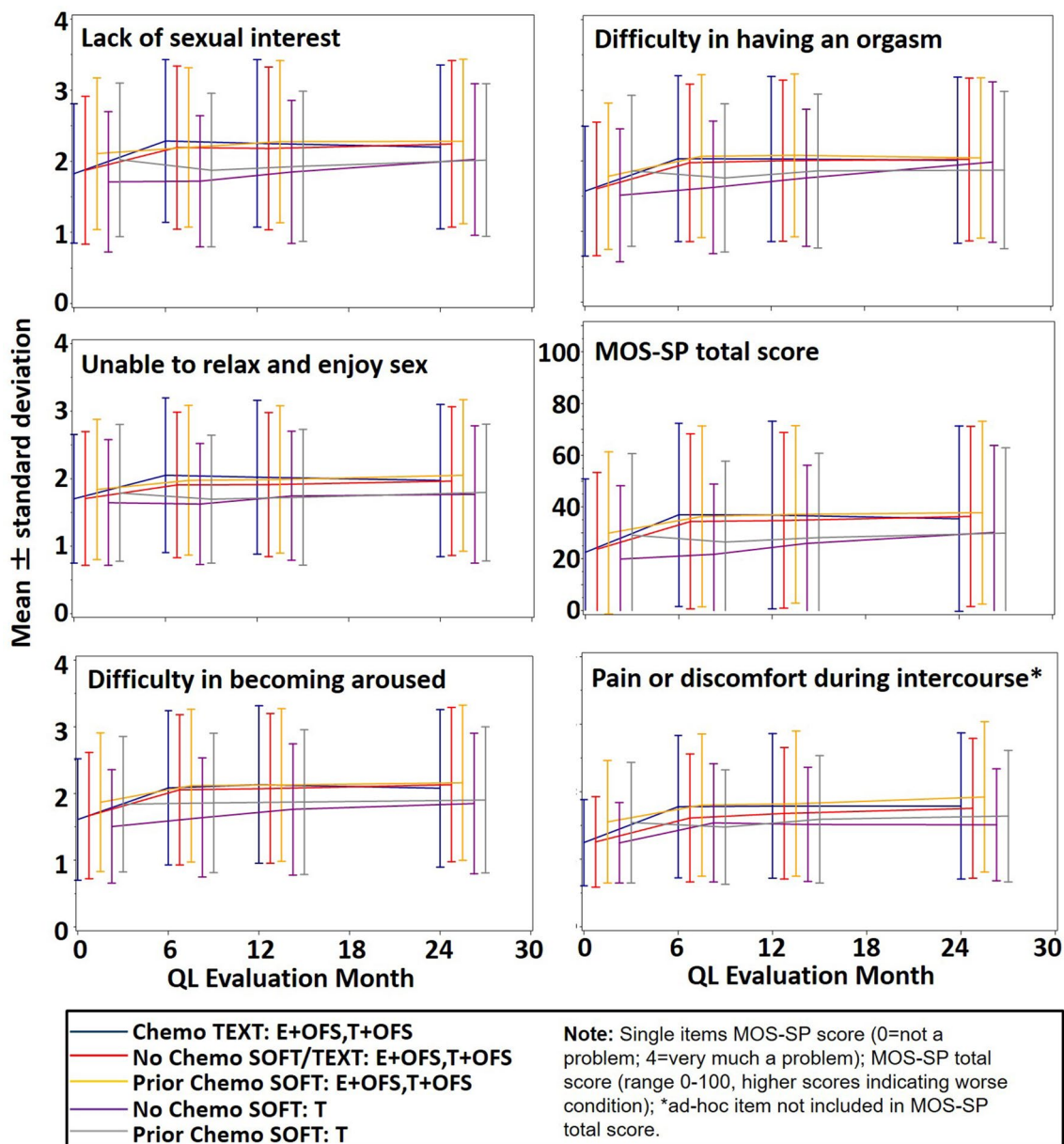
IQR interquartile range, *TEXT* Tamoxifen and Exemestane Trial, *OFS* ovarian function suppression, *E* exemestane, *T* tamoxifen, *SOFT* Suppression of Ovarian Function Trial

Table 2 Percentage of women reporting more than mild problems^a in the four MOS-SP sexual problems domains and with pain/discomfort during intercourse

Assessment time-point	Baseline		Month 6		Month 12		Month 18		Month 24	
	N	%	N	%	N	%	N	%	N	%
Lack of sexual interest	647	28.4	756	36.4	737	37.5	13	36.1	700	38.6
Unable to relax and enjoy sex	498	21.8	580	28.0	573	29.1	11	30.6	539	29.7
Difficulty in becoming aroused	467	20.5	645	31.1	661	33.6	13	36.1	615	33.9
Difficulty in having an orgasm	430	18.9	617	29.7	611	31.1	11	30.6	572	31.5
Pain or discomfort during intercourse	221	9.7	409	19.7	416	21.1	9	25.0	402	22.2

^aPercentage of patients who indicated each item as “somewhat of a problem” or “very much a problem”

MOS-SP Medical Outcome Study-Sexual Problems scale

**Fig. 2** Changes in sexual problems over time: absolute mean values for each cohort at baseline and follow-up time-points for the MOS-SP total score, the MOS-SP individual items and the ad hoc item for pain or discomfort with intercourse. MOS-SP Medical Outcome Study-

Sexual Problems scale, TEXT Tamoxifen and Exemestane Trial, SOFT Suppression of Ovarian Function Trial, OFS ovarian function suppression, E exemestane, T tamoxifen, QL quality-of-life, Chemo Chemotherapy

Table 3 Predictors of sexual problems—across all cohorts

Estimated mean difference between severity groups ^a												
	6 months				12 months				24 months			
	Mean	95% LCL	95% UCL	P value	Mean	95% LCL	95% UCL	P value	Mean	95% LCL	95% UCL	P value
Vaginal dryness	13	10	17	<0.0001	12	9	16	<0.0001	9	5	13	<0.0001
Sleep disturbance	8	5	12	<0.0001	8	4	11	<0.0001	8	4	12	<0.0001
Bone and joint pains	4	0	7	0.0463	6	2	9	0.0051	4	0	9	0.0415
Hot flushes	6	2	10	0.0012	3	-1	7	0.2018	2	-3	6	0.4930
Troubled by weight gain	6	2	9	0.0010	4	0	7	0.0490	3	-1	7	0.1763
Tiredness	5	1	8	0.0084	2	-2	6	0.2757	5	1	9	0.0166
Feeling sick (nausea vomiting)	3	0	6	0.0867	1	-3	4	0.7286	0	-4	4	0.9057
Depression status	6	3	10	0.0005	4	0	8	0.0609	0	-4	5	0.8512
Age group	-1	-6	4	0.7081	3	-2	7	0.3127	-0	-6	5	0.9131

^aSeverity groups for symptoms were defined as “more severe” vs. “less severe” based on median changes between baseline and 6 months, depression status was defined as no depression (CES-D score < 15) vs. depression (CES-D score ≥ 15), age group was defined as < 40 vs. ≥ 40 years

Mean > 0 indicates that the group with more severe symptoms, depression, and had a greater worsening in sexual function than the group with less severe symptoms

LCL Lower Confidence Limit, UCL Upper Confidence Limit

The association of individual endocrine symptoms with changes in sexual problems varied according to cohort. In the two cohorts assigned T-alone, only vaginal dryness in the cohort without chemotherapy (Table S4a), and sleep disturbance in the cohort with prior chemotherapy (Table S4b), predicted sexual problems.

In patients assigned endocrine therapy including OFS, with or without prior chemotherapy, the pattern of symptoms predictive of sexual problems was similar: vaginal dryness was a significant predictor across all time-points, sleep disturbances were associated with sexual problems up to one year of treatment, hot flushes and being troubled by weight gain up to 6 months (Table S4c and S4d). In those who had no prior chemotherapy, tiredness and bone or joint pain also predicted sexual problems at some time-points (Table S4d).

Among patients assigned OFS who received concurrent chemotherapy followed by oral endocrine therapy, tiredness predicted sexual problems up to 6 months, and vaginal dryness, sleep disturbances, hot flushes predicted sexual problems up to 12 months (Table S4e). These associations disappeared at 24 months.

The association of depression status at 6 months with changes in sexual problems was tested with the same mixed models by adding the two most significant endocrine symptoms (severity of change in vaginal dryness and sleep disturbance). Across cohorts, patients meeting the cut-off for a depression (scores ≥ 15) showed a greater worsening in sexual problems in the short-term than those considered to have no depression (Table 3). Looking at the different cohorts, depression at 6 months predicted sexual problems at 24 months in patients who were assigned T-only (hypothesis 2, Table S4a), at 6 months in patients with prior chemotherapy and tamoxifen (Table S4b), and at 12 months in patients who were assigned concurrent chemotherapy and endocrine therapy plus OFS (Table S4e). Of the 2287 patients, 574 patients (25%) were receiving an anti-depressant at the 6 months assessment. A summary of depression status by use of anti-depressant is provided in the supplementary material (Table S5). When controlling for the use of anti-depressants during the first 6 months, results were similar (data not shown).

Mixed models including the five cohorts were applied to test changes in sexual problems over time for the different age groups (< 35, 35–39, 40–44, 45–49, 50+). Figure 3 shows that differences in changes were similar and not clinically meaningful. Age (dichotomized as < 40 vs. ≥ 40) did not significantly predict difference in worsening of sexual problems (hypothesis 3, Table 3).

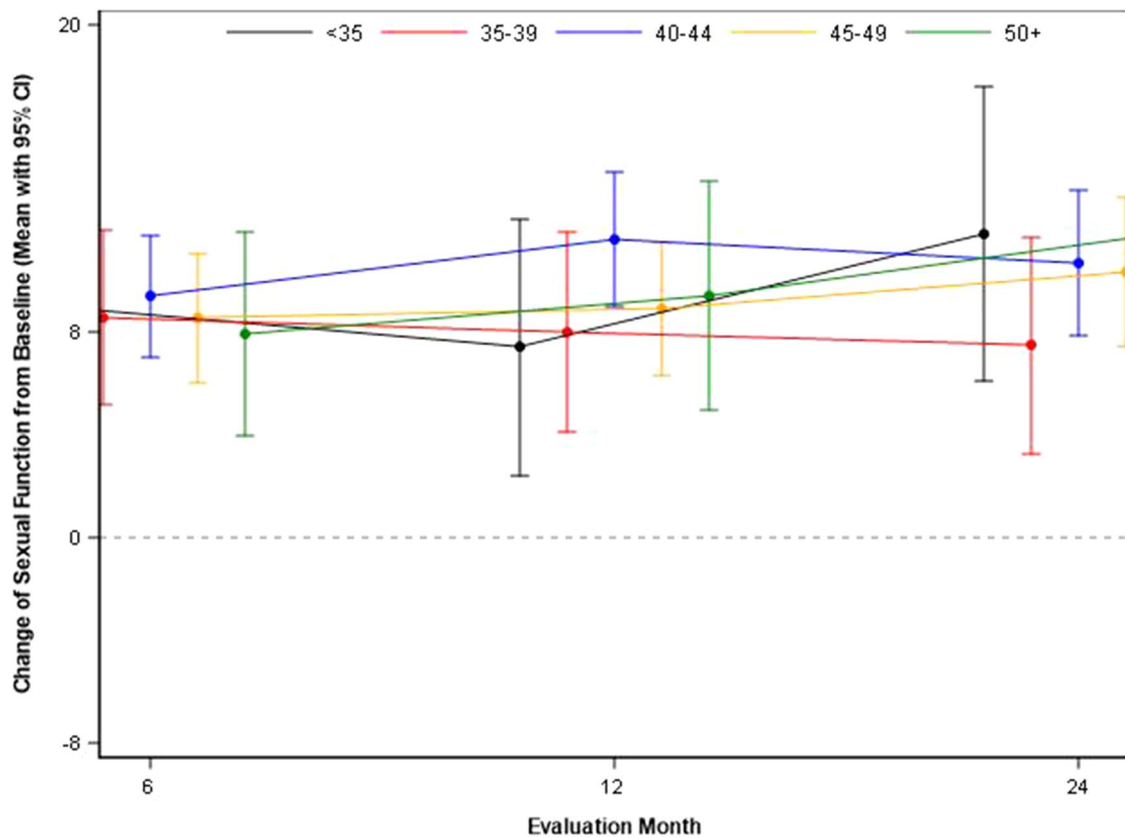


Fig. 3 Changes in sexual problems (MOS-SP total score) over time by age group: *MOS-SP* Medical Outcome Study-Sexual Problems scale, *CI* confidence interval

Discussion

In this large sample of premenopausal women undergoing adjuvant oral endocrine therapy with or without OFS, sexual problems increased to a clinically relevant extent up to 6 months after treatment start and persisted at this level during the first 2 years. Patients assigned OFS in addition to oral endocrine therapy reported the most pronounced, clinically meaningful, worsening, irrespective of the receipt of chemotherapy.

Relatively little longitudinal data on changes in sexual functioning are available for premenopausal women. Lee et al. reported that the proportion of patients experiencing sexual dysfunction was significantly higher after at least 12 months of chemo- or endocrine therapy using a gonadotropin releasing hormone agonist than before diagnosis [19]. In a large cohort of young breast cancer survivors, five distinct trajectories of sexual functioning were identified, all predicted by ovaries suppressed or removed. Stable, mild symptoms characterized the most common trajectory [47]. These results are not directly comparable to ours due to diverging population and treatments; though support that OFS has a pronounced negative effect

on sexual function, irrespective of timing and treatment with chemotherapy.

Our first hypothesis regarding selected symptoms as predictors for sexual problems was confirmed for vaginal dryness, sleep disturbances and bone or joint pain. The negative impact of vaginal dryness on sexual problems is in line with results from previous studies [31, 48]. The negative consequences of sleep deprivation on sexuality is intuitively understandable. Greater musculoskeletal pain predicted poorer sexual functioning in young breast cancer survivors [47], likely due to the loss of estrogen. Our results indicate that if a woman reports treatment-induced musculoskeletal pain, she may also have sexual problems. Whether interventions that ameliorate AI-associated arthralgia [49, 50] may translate in better sexual function was not investigated. In summary, depending on therapy, only a few different symptoms may be associated with sexual problems. Distinct interventions for their improvement may be required [51], which in turn may mitigate sexual problems.

A number of studies have reported association between depressive symptoms and sexual problems [9, 18], sexual inactivity [19] or a hypoactive sexual desire disorder [28] in breast cancer survivors and in the general population [52,

53]. In contrast to our hypothesis, in the overall population, depression status at 6 months was associated with sexual problems at this time-point, but not over 2 years. The use of anti-depressants complicates the interpretation of the association between depression and sexual problems, given that they may be a side effect, depending on the specific anti-depressant drug used [54]. Our results did not change when controlling for the use of anti-depressants during the first 6 months of trial treatment. In contrast to most of the studies on sexuality in women with breast cancer, we investigated depression as predictor for sexual problems within a large-scale prospective randomized controlled trial. Although this approach is superior to cross-sectional and cohort studies to investigate causal relationships, an inverse cause-effect relationship between sexual problems and depression cannot be excluded.

It has been suggested that women between 40 and 60 years report worse sexual functioning than younger or older cohorts [8, 35]. Our hypothesis that younger women will report greater worsening of sexual problems than older premenopausal women was not confirmed. Although the age cut-off may be arbitrary, in another subgroup analysis of TEXT/SOFT of women younger than 35 years [55], their levels of loss of sexual interest and arousal problems were similar to those of older premenopausal women [55].

When we started to develop TEXT/SOFT almost two decades ago, there was no brief self-report measure of sexual function that could be recommended for the use in the oncology setting [56]. The MOS-SP was selected as a subscale covering only three of the five sexual dimensions defined by internationally accepted diagnostic criteria, [57, 58] and without providing a predefined cut-off for sexual disorder, as with other tools [7]. We cannot estimate if the level of sexual problems reported meets the definition of a disorder. Recoding the answer of those women who responded to a MOS-SP item with “not applicable” to “not a problem” may underestimate the severity of sexual problems. Sexual problems of women who are not sexually active because of treatment-related problems and choose to answer with “not applicable” are not adequately captured. The MOS-SP does not cover sexual distress, a criterion added to the diagnostic criteria of sexual dysfunction, which has been considered controversial since then [59]. Because the MOS-SP was designed to be applicable for persons without a partner or who were not sexually active during the period of interest, we did not distinguish according to sexual activity. This approach is supported by a study, in which partnered breast cancer survivors who had been sexually inactive reported less interest in sex and were at least sometimes dissatisfied with their sex life [18].

Although we controlled for disease and patient characteristics, further psychological (e.g., anxiety, relationship with partner, body image) [47] or biological factors, such

as serum hormone levels [60], thyroid dysfunction [19], and bilateral mastectomy [61, 62] may be potential risk factors for sexual dysfunction. We assessed sexual problems during the first two of 5 years of treatment with an intention-to-treat approach. Some of the patients may not have continued with their assigned treatment due to side effects, and sexual problems to various degrees may persist for a longer period [47].

In conclusion, premenopausal women undergoing adjuvant endocrine therapy including OFS experience sexual problems up to 2 years on treatment. Among several key symptoms related to endocrine therapy, vaginal dryness, sleep disturbances and bone and joint pains significantly predicted sexual problems during these 2 years. All other symptoms had a smaller impact on changes of sexual problems and varied according to cohort. Early identification of these treatment-related symptoms may contribute to initiate timely and tailored interventions.

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Data availability The data on which these analyses are based forms part of the clinical trials database of the International Breast Cancer Study Group, and as such is available for use on application in accordance with IBCSG data sharing policy.

Compliance with ethical standards

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Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Ethics committees and appropriate national health authorities from each center approved the protocol, and all patients provided written informed consent as part of the informed consent for the main trial. This manuscript does not contain any individual person's data in any form.

References

1. Bober SL, Varela VS (2012) Sexuality in adult cancer survivors: challenges and intervention. *J Clin Oncol* 30(30):3712–3719. <https://doi.org/10.1200/JCO.2012.41.7915>
2. Schover LR, van der Kaaij M, van Dorst E, Creutzberg C, Huyghe E, Kiserud CE (2014) Sexual dysfunction and infertility as late effects of cancer treatment. *EJC Suppl* 12(1):41–53. <https://doi.org/10.1016/j.ejcsup.2014.03.004>
3. Kedde H, van de Wiel HB, Weijmar Schultz WC, Wijnen C (2013) Sexual dysfunction in young women with breast cancer. *Support Care Cancer* 21(1):271–280. <https://doi.org/10.1007/s00520-012-1521-9>
4. Baumgart J, Nilsson K, Evers AS, Kallak TK, Poromaa IS (2013) Sexual dysfunction in women on adjuvant endocrine therapy after breast cancer. *Menopause* 20(2):162–168. <https://doi.org/10.1097/gme.0b013e31826560da>
5. Frechette D, Paquet L, Verma S, Clemons M, Wheatley-Price P, Gertler SZ, Song X, Graham N, Dent S (2013) The impact of endocrine therapy on sexual dysfunction in postmenopausal women with early stage breast cancer: encouraging results from a prospective study. *Breast Cancer Res Treat* 141(1):111–117. <https://doi.org/10.1007/s10549-013-2659-y>
6. Raggio GA, Butryn ML, Arigo D, Mikorski R, Palmer SC (2014) Prevalence and correlates of sexual morbidity in long-term breast cancer survivors. *Psychol Health* 29(6):632–650. <https://doi.org/10.1080/08870446.2013.879136>
7. Maiorino MI, Chiodini P, Bellastella G, Giugliano D, Esposito K (2016) Sexual dysfunction in women with cancer: a systematic review with meta-analysis of studies using the Female Sexual Function Index. *Endocrine* 54(2):329–341. <https://doi.org/10.1007/s12020-015-0812-6>
8. Davis SR, Panjari M, Robinson PJ, Fradkin P, Bell RJ (2014) Menopausal symptoms in breast cancer survivors nearly 6 years after diagnosis. *Menopause* 21(10):1075–1081. <https://doi.org/10.1097/GME.0000000000000219>
9. Oberguggenberger A, Martini C, Huber N, Fallowfield L, Hubalek M, Daniaux M, Sperner-Unterwieser B, Holzner B, Sztankay M, Gamper E, Meraner V (2017) Self-reported sexual health: breast cancer survivors compared to women from the general population—an observational study. *BMC Cancer* 17(1):599. <https://doi.org/10.1186/s12885-017-3580-2>
10. Aerts L, Christiaens MR, Enzlin P, Neven P, Amant F (2014) Sexual functioning in women after mastectomy versus breast conserving therapy for early-stage breast cancer: a prospective controlled study. *Breast* 23(5):629–636. <https://doi.org/10.1016/j.breast.2014.06.012>
11. Boquiren VM, Esplen MJ, Wong J, Toner B, Warner E, Malik N (2016) Sexual functioning in breast cancer survivors experiencing body image disturbance. *Psychooncology* 25(1):66–76. <https://doi.org/10.1002/pon.3819>
12. Schover LR (2008) Premature ovarian failure and its consequences: vasomotor symptoms, sexuality, and fertility. *J Clin Oncol* 26(5):753–758. <https://doi.org/10.1200/JCO.2007.14.1655>
13. Rosenberg SM, Tamimi RM, Gelber S, Ruddy KJ, Bober SL, Kerekoglow S, Borges VF, Come SE, Schapira L, Partridge AH (2014) Treatment-related amenorrhea and sexual functioning in young breast cancer survivors. *Cancer* 120(15):2264–2271. <https://doi.org/10.1002/cncr.28738>
14. Berglund G, Nystedt M, Bolund C, Sjoden PO, Rutquist LE (2001) Effect of endocrine treatment on sexuality in premenopausal breast cancer patients: a prospective randomized study. *J Clin Oncol* 19(11):2788–2796. <https://doi.org/10.1200/JCO.2001.19.11.2788>

15. Bernhard J, Luo W, Ribi K, Colleoni M, Burstein HJ, Tondini C, Pinotti G, Spazzapan S, Ruhstaller T, Puglisi F, Pavesi L, Parmar V, Regan MM, Pagani O, Fleming GF, Francis PA, Price KN, Coates AS, Gelber RD, Goldhirsch A, Walley BA (2015) Patient-reported outcomes with adjuvant exemestane versus tamoxifen in premenopausal women with early breast cancer undergoing ovarian suppression (TEXT and SOFT): a combined analysis of two phase 3 randomised trials. *Lancet Oncol* 16(7):848–858. [https://doi.org/10.1016/S1470-2045\(15\)00049-2](https://doi.org/10.1016/S1470-2045(15)00049-2)
16. Tevaarwerk AJ, Wang M, Zhao F, Fetting JH, Cella D, Wagner LI, Martino S, Ingle JN, Sparano JA, Solin LJ, Wood WC, Robert NJ (2014) Phase III comparison of tamoxifen versus tamoxifen plus ovarian function suppression in premenopausal women with node-negative, hormone receptor-positive breast cancer (E-3193, INT-0142): a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 32(35):3948–3958. <https://doi.org/10.1200/JCO.2014.55.6993>
17. Ribi K, Luo W, Bernhard J, Francis PA, Burstein HJ, Ciruelos E, Bellet M, Pavesi L, Lluch A, Visini M, Parmar V, Tondini C, Kerbrat P, Perello A, Neven P, Torres R, Lombardi D, Puglisi F, Karlsson P, Ruhstaller T, Colleoni M, Coates AS, Goldhirsch A, Price KN, Gelber RD, Regan MM, Fleming GF (2016) Adjuvant tamoxifen plus ovarian function suppression versus tamoxifen alone in premenopausal women with early breast cancer: patient-reported outcomes in the suppression of ovarian function trial. *J Clin Oncol* 34(14):1601–1610. <https://doi.org/10.1200/JCO.2015.64.8675>
18. Avis NE, Johnson A, Canzona MR, Levine BJ (2018) Sexual functioning among early post-treatment breast cancer survivors. *Support Care Cancer* 26(8):2605–2613. <https://doi.org/10.1007/s00520-018-4098-0>
19. Lee M, Kim YH, Jeon MJ (2015) Risk factors for negative impacts on sexual activity and function in younger breast cancer survivors. *Psychooncology* 24(9):1097–1103. <https://doi.org/10.1002/pon.3772>
20. Speer JJ, Hillenberg B, Sugrue DP, Blacker C, Kresge CL, Decker VB, Zakalik D, Decker DA (2005) Study of sexual functioning determinants in breast cancer survivors. *Breast J* 11(6):440–447. <https://doi.org/10.1111/j.1075-122X.2005.00131.x>
21. Bredart A, Dolbeault S, Savignoni A, Besancenot C, This P, Giami A, Michaels S, Flahault C, Falcou MC, Asselain B, Copel L (2011) Prevalence and associated factors of sexual problems after early-stage breast cancer treatment: results of a French exploratory survey. *Psychooncology* 20(8):841–850. <https://doi.org/10.1002/pon.1789>
22. Landi SN, Doll KM, Bensen JT, Hendrix L, Anders CK, Wu JM, Nichols HB (2016) Endocrine therapy and urogenital outcomes among women with a breast cancer diagnosis. *Cancer Causes Control* 27(11):1325–1332. <https://doi.org/10.1007/s10552-016-0810-x>
23. Soldara SV, Ennis M, Lohmann AE, Goodwin PJ (2018) Sexual health in long-term breast cancer survivors. *Breast Cancer Res Treat.* <https://doi.org/10.1007/s10549-018-4894-8>
24. Perez M, Liu Y, Schootman M, Aft RL, Schechtman KB, Gillanders WE, Jeffe DB (2010) Changes in sexual problems over time in women with and without early-stage breast cancer. *Menopause* 17(5):924–937. <https://doi.org/10.1097/gme.0b013e3181d5dd26>
25. Marino JL, Saunders CM, Emery LI, Green H, Doherty DA, Hickey M (2016) How does adjuvant chemotherapy affect menopausal symptoms, sexual function, and quality of life after breast cancer? *Menopause* 23(9):1000–1008. <https://doi.org/10.1097/GME.0000000000000664>
26. Panjari M, Bell RJ, Davis SR (2011) Sexual function after breast cancer. *J Sex Med* 8(1):294–302. <https://doi.org/10.1111/j.1743-6109.2010.02034.x>
27. van Londen GJ, Beckjord EB, Dew MA, Cooper KL, Davidson NE, Bovbjerg DH, Donovan HS, Thurston RC, Morse JQ, Nutt S, Recheis R (2014) Associations between adjuvant endocrine therapy and onset of physical and emotional concerns among breast cancer survivors. *Support Care Cancer* 22(4):937–945. <https://doi.org/10.1007/s00520-013-2041-y>
28. Hummel SB, Hahn DEE, van Lankveld J, Oldenburg HSA, Broomans E, Aaronson NK (2017) Factors associated with specific diagnostic and statistical manual of mental disorders, fourth edition sexual dysfunctions in breast cancer survivors: a study of patients and their partners. *J Sex Med* 14(10):1248–1259. <https://doi.org/10.1016/j.jsxm.2017.08.004>
29. Robinson PJ, Bell RJ, Christakis MK, Ivezic SR, Davis SR (2017) Aromatase inhibitors are associated with low sexual desire causing distress and fecal incontinence in women: an observational study. *J Sex Med* 14(12):1566–1574. <https://doi.org/10.1016/j.jsxm.2017.09.018>
30. Gandhi C, Butler E, Pesek S, Kwait R, Edmonson D, Raker C, Clark MA, Stuckey A, Gass J (2019) Sexual dysfunction in breast cancer survivors: is it surgical modality or adjuvant therapy? *Am J Clin Oncol* 42(6):500–506. <https://doi.org/10.1097/COC.0000000000000552>
31. Burwell SR, Case LD, Kaelin C, Avis NE (2006) Sexual problems in younger women after breast cancer surgery. *J Clin Oncol* 24(18):2815–2821. <https://doi.org/10.1200/JCO.2005.04.2499>
32. Paiva CE, Rezende FF, Paiva BS, Mauad EC, Zucca-Matthes G, Carnesecca EC, Syrjanen KJ, Schover LR (2016) Associations of body mass index and physical activity with sexual dysfunction in breast cancer survivors. *Arch Sex Behav* 45:2057–2068. <https://doi.org/10.1007/s10508-016-0758-7>
33. Rojas KE, Matthews N, Raker C, Clark MA, Onstad M, Stuckey A, Gass J (2018) Body mass index (BMI), postoperative appearance satisfaction, and sexual function in breast cancer survivorship. *J Cancer Surviv* 12(1):127–133. <https://doi.org/10.1007/s11764-017-0651-y>
34. Den Ouden BL, Van Heck GL, Van der Steeg AF, Roukema JA, De Vries J (2010) Clinical factors are not the best predictors of quality of sexual life and sexual functioning in women with early stage breast cancer. *Psychooncology* 19(6):646–656. <https://doi.org/10.1002/pon.1610>
35. Morrow PK, Broxson AC, Munsell MF, Basen-Enquist K, Rosenblum CK, Schover LR, Nguyen LH, Hsu L, Castillo L, Hahn KM, Litton JK, Kwiatkowski DN, Hortobagyi GN (2014) Effect of age and race on quality of life in young breast cancer survivors. *Clin Breast Cancer* 14(2):e21–31. <https://doi.org/10.1016/j.clbc.2013.10.003>
36. Pagani O, Regan MM, Walley BA, Fleming GF, Colleoni M, Lang I, Gomez HL, Tondini C, Burstein HJ, Perez EA, Ciruelos E, Stearns V, Bonnefoi HR, Martino S, Geyer CE Jr, Pinotti G, Puglisi F, Crivellari D, Ruhstaller T, Winer EP, Rabaglio-Poretti M, Maibach R, Ruepp B, Giobbie-Hurder A, Price KN, Bernhard J, Luo W, Ribi K, Viale G, Coates AS, Gelber RD, Goldhirsch A, Francis PA, TEXT, and SOFT Investigators; International Breast Cancer Study Group (2014) Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med* 371(2):107–118. <https://doi.org/10.1056/NEJMoa1404037>
37. Francis PA, Regan MM, Fleming GF, Lang I, Ciruelos E, Bellet M, Bonnefoi HR, Climent MA, Da Prada GA, Burstein HJ, Martino S, Davidson NE, Geyer CE Jr, Walley BA, Coleman R, Kerbrat P, Buchholz S, Ingle JN, Winer EP, Rabaglio-Poretti M, Maibach R, Ruepp B, Giobbie-Hurder A, Price KN, Colleoni M, Viale G, Coates AS, Goldhirsch A, Gelber RD, SOFT Investigators; International Breast Cancer Study Group (2015) Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med* 372(5):436–446. <https://doi.org/10.1056/NEJMoa1412379>

38. Sherbourne CD (1992) Social functioning: sexual problems measures. In: Stewart AL, Ware JE (eds) *Measuring functioning and well-being: the medical outcomes study approach*. Duke University Press, Durham, pp 194–204
39. Bartula I, Sherman KA (2013) Screening for sexual dysfunction in women diagnosed with breast cancer: systematic review and recommendations. *Breast Cancer Res Treat* 141(2):173–185. <https://doi.org/10.1007/s10549-013-2685-9>
40. Ganz PA, Cecchini RS, Julian TB, Margolese RG, Costantino JP, Vallow LA, Albain KS, Whitworth PW, Cianfrocca ME, Brufsky AM, Gross HM, Soori GS, Hopkins JO, Fehrenbacher L, Sturtz K, Wozniak TF, Seay TE, Mamounas EP, Wolmark N (2016) Patient-reported outcomes with anastrozole versus tamoxifen for postmenopausal patients with ductal carcinoma in situ treated with lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial. *Lancet* 387(10021):857–865. [https://doi.org/10.1016/S0140-6736\(15\)01169-1](https://doi.org/10.1016/S0140-6736(15)01169-1)
41. Sloan JA, Dueck A (2004) Issues for statisticians in conducting analyses and translating results for quality of life end points in clinical trials. *J Biopharm Stat* 14(1):73–96. <https://doi.org/10.1081/BIP-120028507>
42. Bernhard J, Hurny C, Coates AS, Peterson HF, Castiglione-Gertsch M, Gelber RD, Goldhirsch A, Senn HJ, Rudenstam CM (1997) Quality of life assessment in patients receiving adjuvant therapy for breast cancer: the IBCSG approach. The International Breast Cancer Study Group. *Ann Oncol* 8(9):825–835. <https://doi.org/10.1023/A:1008269715091>
43. Bernhard J, Sullivan M, Hurny C, Coates AS, Rudenstam CM (2001) Clinical relevance of single item quality of life indicators in cancer clinical trials. *Br J Cancer* 84(9):1156–1165. <https://doi.org/10.1054/bjoc.2001.1785>
44. Bernhard J, Zahrieh D, Castiglione-Gertsch M, Hurny C, Gelber RD, Forbes JF, Murray E, Collins J, Aebi S, Thurlimann B, Price KN, Goldhirsch A, Coates AS, International Breast Cancer Study Group Trial V (2007) Adjuvant chemotherapy followed by goserelin compared with either modality alone: the impact on amenorrhea, hot flashes, and quality of life in premenopausal patients—the International Breast Cancer Study Group Trial VIII. *J Clin Oncol* 25(3):263–270. <https://doi.org/10.1200/JCO.2005.04.5393>
45. Radloff LS (1977) The CES-D Scale: a self-reported depression scale for research in the general population. *Appl Psychol Meas* 1:385–401
46. Wakefield CE, Butow PN, Aaronson NA, Hack TF, Hulbert-Williams NJ, Jacobsen PB, International Psycho-Oncology Society Research Committee (2015) Patient-reported depression measures in cancer: a meta-review. *Lancet Psychiatry* 2(7):635–647. [https://doi.org/10.1016/S2215-0366\(15\)00168-6](https://doi.org/10.1016/S2215-0366(15)00168-6)
47. von Hippel C, Rosenberg SM, Austin SB, Sprunck-Harrild K, Ruddy KJ, Schapira L, Come S, Borges VF, Partridge AH (2019) Identifying distinct trajectories of change in young breast cancer survivors' sexual functioning. *Psychooncology* 28(5):1033–1040. <https://doi.org/10.1002/pon.5047>
48. Ganz PA, Desmond KA, Belin TR, Meyerowitz BE, Rowland JH (1999) Predictors of sexual health in women after a breast cancer diagnosis. *J Clin Oncol* 17(8):2371–2380. <https://doi.org/10.1200/JCO.1999.17.8.2371>
49. Henry NL, Unger JM, Schott AF, Fehrenbacher L, Flynn PJ, Prow DM, Sharer CW, Burton GV, Kuzma CS, Moseley A, Lew DL, Fisch MJ, Moinpour CM, Hershman DL, Wade JL 3rd (2018) Randomized, multicenter, placebo-controlled clinical trial of duloxetine versus placebo for aromatase inhibitor-associated arthralgias in early-stage breast cancer: SWOG S1202. *J Clin Oncol* 36(4):326–332. <https://doi.org/10.1200/JCO.2017.74.6651>
50. Irwin ML, Cartmel B, Gross CP, Ercolano E, Li F, Yao X, Fiellin M, Capozza S, Rothbard M, Zhou Y, Harrigan M, Sanft T, Schmitz K, Neogi T, Hershman D, Ligibel J (2015) Randomized exercise trial of aromatase inhibitor-induced arthralgia in breast cancer survivors. *J Clin Oncol* 33(10):1104–1111. <https://doi.org/10.1200/JCO.2014.57.1547>
51. Carter J, Lacchetti C, Andersen BL, Barton DL, Bolte S, Damast S, Diefenbach MA, DuHamel K, Florendo J, Ganz PA, Goldfarb S, Hallmeyer S, Kushner DM, Rowland JH (2018) Interventions to address sexual problems in people with cancer: American Society of Clinical Oncology Clinical Practice Guideline Adaptation of Cancer Care Ontario Guideline. *J Clin Oncol* 36(5):492–511. <https://doi.org/10.1200/JCO.2017.75.8995>
52. Hayes RD, Dennerstein L, Bennett CM, Sidat M, Gurrin LC, Fairley CK (2008) Risk factors for female sexual dysfunction in the general population: exploring factors associated with low sexual function and sexual distress. *J Sex Med* 5(7):1681–1693. <https://doi.org/10.1111/j.1743-6109.2008.00838.x>
53. Brotto L, Atallah S, Johnson-Agbakwu C, Rosenbaum T, Abdo C, Byers ES, Graham C, Nobre P, Wylie K (2016) Psychological and interpersonal dimensions of sexual function and dysfunction. *J Sex Med* 13(4):538–571. <https://doi.org/10.1016/j.jsxm.2016.01.019>
54. Reichenpader U, Gartlehner G, Morgan LC, Greenblatt A, Nussbaumer B, Hansen RA, Van Noord M, Lux L, Gaynes BN (2014) Sexual dysfunction associated with second-generation antidepressants in patients with major depressive disorder: results from a systematic review with network meta-analysis. *Drug Saf* 37(1):19–31. <https://doi.org/10.1007/s40264-013-0129-4>
55. Saha P, Regan MM, Pagani O, Francis PA, Walley BA, Ribí K, Bernhard J, Luo W, Gomez HL, Burstein HJ, Parmar V, Torres R, Stewart J, Bellet M, Perello A, Dane F, Moreira A, Vorobiof D, Nottage M, Price KN, Coates AS, Goldhirsch A, Gelber RD, Colleoni M, Fleming GF, SOFT; TEXT Investigators; International Breast Cancer Study Group (2017) Treatment efficacy, adherence, and quality of life among women younger than 35 years in the international breast cancer study group TEXT and SOFT adjuvant endocrine therapy trials. *J Clin Oncol* 35(27):3113–3122. <https://doi.org/10.1200/JCO.2016.72.0946>
56. Jeffery DD, Tzeng JP, Keefe FJ, Porter LS, Hahn EA, Flynn KE, Reeve BB, Weinfurt KP (2009) Initial report of the cancer Patient-Reported Outcomes Measurement Information System (PROMIS) sexual function committee: review of sexual function measures and domains used in oncology. *Cancer* 115(6):1142–1153. <https://doi.org/10.1002/cncr.24134>
57. American Psychiatric Association (2013) *Diagnostic and statistical manual of mental disorders*. American Psychiatric Association, Washington DC
58. World Health Organization (2004) *International classification of diseases and health related problems*. World Health Organization, Geneva
59. Hendrickx L, Gijs L, Enzlin P (2013) Distress, sexual dysfunctions, and DSM: dialogue at cross purposes? *J Sex Med* 10(3):630–641. <https://doi.org/10.1111/j.1743-6109.2012.02971.x>
60. Safarinejad MR, Shafiei N, Safarinejad S (2013) Quality of life and sexual functioning in young women with early-stage breast cancer 1 year after lumpectomy. *Psychooncology* 22(6):1242–1248. <https://doi.org/10.1002/pon.3130>
61. Razdan SN, Patel V, Jewell S, McCarthy CM (2016) Quality of life among patients after bilateral prophylactic mastectomy: a systematic review of patient-reported outcomes. *Qual Life Res* 25(6):1409–1421. <https://doi.org/10.1007/s11136-015-1181-6>
62. Bai L, Arver B, Johansson H, Sandelin K, Wickman M, Brandberg Y (2019) Body image problems in women with and without breast cancer 6–20 years after bilateral risk-reducing surgery—a prospective follow-up study. *Breast* 44:120–127. <https://doi.org/10.1016/j.breast.2019.01.013>

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