

ORIGINAL ARTICLE

Quality of life in long-term premenopausal early-stage breast cancer survivors from Spain. Effects of surgery and time since surgery

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Summary

Purpose: More research is needed into Quality of Life (QoL) in young early-stage breast cancer patients in the long-term. Knowledge of long-term effects of surgery on QoL in breast cancer patients is limited. The purpose of this study was to assess QoL in premenopausal Spanish early-stage breast cancer patients over a long follow-up period and evaluate differences among surgery-treated groups and the influence of time on patient QoL.

Methods: 243 premenopausal stage I-III relapse-free breast cancer patients completed the EORTC QLQ-C30 and QLQ-BR23 questionnaire once during follow-up (5-20 years after surgery). Univariate and multivariate logistic regression analyses were performed to estimate the results.

Results: QoL mean scores were high in most areas (>80

points in functioning; <20 points in symptoms areas). Limitations were moderate (>30 points) in global QoL, sleep disturbance, future perspective, sexual areas, and hot flashes. Mastectomized patients had a 4-fold greater risk of low scores in body image. Patients with a longer follow-up showed lower systemic side effects, hot flashes and breast symptoms.

Conclusions: QoL in Spanish premenopausal early-stage breast cancer patients in a long follow-up after surgery is high. Differences in QoL among surgery-treated groups are limited. Time since surgery influences treatment side effects.

Key words: breast cancer, EORTC, premenopausal, quality of life, survivors

Introduction

The National Cancer Institute reports that QoL is a key aspect of cancer survivorship [1]. Recently attention has shifted in Oncology from short-term symptoms and treatment side effects to sequelae that can persist long after treatment has ended and negatively impact QoL [2]. QoL in survivors is an important health indicator since it can help improve function and predict survival [3].

The late effects of cancer and treatment on the QoL of breast cancer patients are a major focus

in research and clinical practice. However, more research is needed into long-term QoL in women with breast cancer [4].

Tian et al. [5] consider it important to study long-term QoL in patients with better prognosis (e.g. early-stage breast cancer patients) since there may be a burden of morbidity years after treatment.

The survival rate of premenopausal breast cancer patients has improved in the last two de-

acades. The QoL of premenopausal breast cancer survivors can be hampered by aspects common to other tumor sites (e.g. fear of recurrence) as well as those specific to breast cancer, such as premature menopause or negative psychosocial effects (e.g. limitations in social relationships) [6]. Koch et al. [7] reported that the youngest breast cancer survivors experienced the highest levels of QoL restrictions: their tumors were more aggressive and patients were generally offered multi-modal therapies, which are often more toxic [8].

Moreover, patients' views on QoL can be influenced by age and experience. Bloom et al. [8] reported that younger patients may have higher expectations for their physical and functional status than elderly ones, which may make them believe their QoL is lower. Some studies have found lower QoL scores in young early-stage breast cancer survivors than in patients over 50 in general (e.g. emotional and social functioning) and specific (e.g. breast symptoms or body image) QoL areas [5,9]. Murthy et al. [10] believed more QoL research is needed into this vulnerable population of young breast cancer survivors.

Numerous studies have analysed the differences between breast-conserving surgery and mastectomy near the time of surgery. Some of them involved early-stage breast cancer patients [11]. However, knowledge of the long-term effects of surgery on QoL in these patients is limited [12]. Although several studies have involved a median follow-up after surgery of 1–5 years [5], it is important to assess long-term differences since these may only become fully apparent in the long term [12].

Cross-cultural differences are found in QoL among breast cancer survivors [13]. QoL studies in different cultural areas could help determine the characteristics of breast cancer survivors in those areas.

To our knowledge, few studies have assessed QoL only in young early-stage breast cancer survivors [14] and none has been conducted in Spain. Moreover, most studies of breast cancer survivors (with different ages and disease stages) have a follow-up period less than 10 years.

In this study we assessed QoL in premenopausal Spanish early-stage breast cancer patients who are in a long-term follow-up period after surgery, evaluated differences among surgery-treated groups, and analysed how time since surgery influences patient QoL.

We expected to find high QoL scores with limitations in physical, social and emotional

areas; differences between groups based on the type of surgery in the same areas as well as in patients with a variety of ages and a shorter follow-up; and a low influence of time since surgery on QoL.

Methods

Participants

A consecutive sample of stage I-IIIa breast cancer patients treated at the Complejo Hospitalario de Navarra, a tertiary metropolitan hospital in Spain, was recruited between September 2011 and January 2014. During this period, follow-up interviews were conducted at the Department of Oncology. Patients were premenopausal when treated. Premenopausal women were identified as those with menses, including those without menses up to the last 6 months but whose plasmatic hormonal levels suggested active ovarian function. Patients were subjected to surgery (mastectomy, breast-conserving surgery) 5–20 years earlier, were disease-free and without relapse or second malignancy during the follow-up period, and may have received adjuvant treatments (radiotherapy, chemotherapy and/or hormotherapy). Radiotherapy was given to patients with conservative surgery and those with mastectomy who fulfilled standard criteria. Patients with a second-line of treatment were excluded.

Measures

All patients completed the QLQ-C30 version 3.0 [15] and QLQ-BR23 [16] EORTC, translated into Spanish in line with the EORTC QoL Study Group translation procedure [17] and validated for use in Spain [18,19].

QLQ-C30 comprises 30 items that assess areas common to different tumor sites and treatments and contains 5 functioning scales (physical, role, emotional, cognitive and social), 8 symptoms scales and/or items (fatigue, nausea/vomiting, pain, dyspnoea, sleep disturbance, appetite loss, constipation and diarrhoea), a financial impact item and a global scale. QLQ-BR23 assesses areas associated with breast cancer and its treatments. It contains 4 functioning scales and/or items (body image, sexual functioning, arm symptoms, future perspective) and 4 symptoms scales and/or items (arm and breast symptoms, systemic therapy side effects and upset by hair loss). Future perspective evaluates patient worries about future health. Scores in all areas range from 0 to 100. Higher scores represent higher functional levels or degrees of symptoms.

Due to their special interest, lymphoedema (an item of *arm symptoms*) and hot flashes (an item of *systemic therapy side effects*) were analysed separately. Sociodemographic and clinical data were obtained from clinical records by the treating oncologists. Patients who answered less than 70% of the QoL items were excluded.

Data collection procedures

Patients matching the inclusion criteria were addressed during one of their follow-up visits. They were interviewed, given oral and written information about the study, and invited to participate. Those who provided informed consent completed the questionnaires once during post-surgery follow-up. After completing the questionnaires, which were self-administered, patients might comment their answers with a psychologist. The study was approved by the Hospital's Ethics Committee and conducted in line with the ethical standards of the Helsinki declaration of 1975, as revised in 2000.

Statistics

Sample characteristics and QoL scores were described using frequencies and percentages for the categorical variables and means and standard deviations for the continuous ones. Scores for the QLQ-C30 and QLQ-BR23 areas were dichotomized for analysis. In most scales the distribution of the QoL areas was skewed towards the high QoL scores (100 points in functional and 0 points in symptoms scales). Due to the large differences in the number of patients per group, groups with 0–50 and > 50 points in the QoL areas could not be compared. QoL scores were dichotomized in high and low levels but a balanced sample of patients was sought in each group.

To assess how time since surgery and type of surgery affected QoL, first univariate logistic regression analyses were performed using the categorized version of QLQ-C30 and QLQ-BR23 areas as response variables and surgery type (conservative, mastectomy) and time since surgery (continuous variable) as explanatory variables. For QoL areas with p value <0.15 on either of the covariates, analyses were complemented with multivariate logistic regression models that included time since surgery and type of surgery as covariates and other adjusting variables, e.g. age at diagnosis, marital status, menopause and limiting comorbidity. The significance of the interaction term between type of surgery and time since surgery was also assessed, and this term was maintained when significant. IBM SPSS Statistics 21 was used for statistical analyses.

Results

Of 259 candidates who attended follow-up interviews at the Hospital's Department of Oncology, 243 patients were evaluated. Reasons for not completing questionnaires were administrative failure (10 cases) and patient refusal (6 cases). Figure 1 shows the number of candidates (650) who satisfied demographic and clinical inclusion criteria during the study period. Of these, 391 did not attend follow-up interviews at the Department

Table 1. Sociodemographic and clinical characteristics of the sample

Characteristics	N	%	Mean	SD
Present age (range 34–68)			54.2	6.8
34–40	4	1.6		
41–45	19	7.7		
46–50	50	20.6		
51–55	68	27.9		
56–60	54	22.3		
61–65	36	14.9		
66–68	12	4.9		
Menopause				
Yes	206	84.8		
No	37	15.2		
Marital status				
Single	31	12.8		
Married	177	72.8		
Widowed	12	4.9		
Separated	23	9.5		
Age when diagnosed (range 28–56)			44.7	5.3
Time since surgery (range 5–20 years)			9.8	4.0
5–9	134	55.2		
10–14	79	32.6		
15–20	30	12.2		
Breast surgery				
Conservative	164	67.5		
Mastectomy	79	32.5		
Without breast reconstruction	20	25.4		
With breast reconstruction	59	74.6		
Axillary surgery				
Lymphadenectomy	192	79.0		
Sentinel node	51	21.0		
Chemotherapy				
Taxanes	8	3.3		
Anthracyclines	76	31.3		
Taxanes + anthracyclines	33	13.6		
Other	70	28.8		
No chemotherapy	56	23.0		
Radiotherapy				
Yes	202	83.1		
No	41	16.9		
Endocrine therapy				
Tamoxifen	147	60.5		
LH-RH analogues	4	1.6		
No	70	28.8		
Other	2	0.9		
Tamoxifen + LH-RH analogues	20	8.2		
Limiting comorbidity				
Yes	38	15.6		
No	205	84.4		

LH-RH: Luteinizing hormone releasing hormone

of Oncology during the study period. There were no significant differences in demographic, disease or treatment characteristics between patients who attended follow-up interviews and those who did not, or between patients with follow-up interviews who did or did not complete the questionnaires. All questionnaires included in the study had over 70% of items answered. Table 1 shows the sociodemographic and clinical characteristics of the patients.

Table 2 shows that mean scores were high in most QoL areas (>80 points in functioning; <20 points in symptoms areas). Limitations were moderate in global QoL, sleep disturbance, future perspective, sexual functioning and enjoyment, and hot flashes (affectation >30 points). Light affectation (20–29 points) was found in emotional functioning, fatigue, pain, and systemic therapy side effects.

Table 3 shows QoL areas found to be related to the type of surgery. Univariate analysis identified body image and social functioning, with p values <0.001 and 0.005, respectively, as statistically significant, whereas arm symptoms had p=0.130. In all three cases, the risk of low QoL was higher in patients who underwent radical surgery, with odds ratio (OR)=2.58 (95%CI: 1.32, 5.04), 4.51 (95%CI: 2.30, 8.83) and 1.72 (95%CI: 0.85,3.49), respectively. Significance was maintained in the multivariate analysis for body image (OR=4.28; 95%CI: 2.14,8.56) but not for the other two areas (p=0.124 for social functioning and p=0.120 for arm symptoms). The greater risk of worse QoL for patients with radical surgery did not vary with

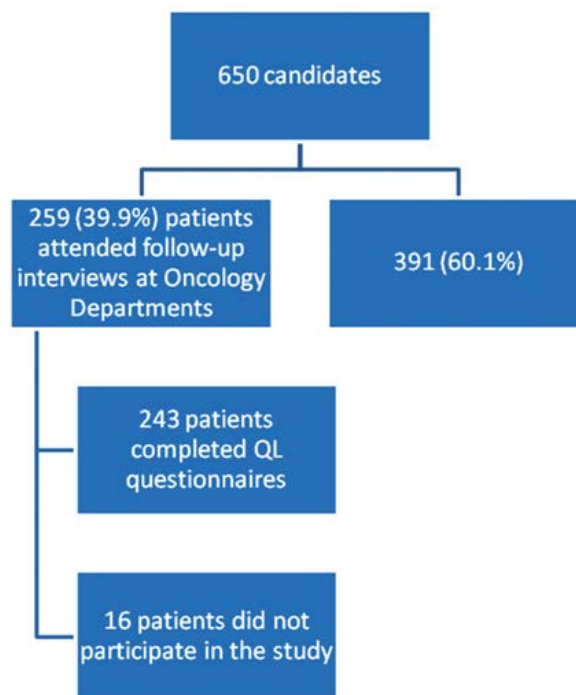


Figure 1. Patients participating in the study. Candidates: number of patients from our province who satisfied the clinical and demographic criteria during the period of study. Follow-up interview at Oncology Departments: candidates who attended follow-up interviews during the period of the study at the Oncology Departments of the Hospital. Completed QoL questionnaires: candidates who attended follow-up interviews at the Hospital and agreed to participate in the study. 391 did not attend follow-up interviews at the Oncology Department during the study period.

time since surgery (the interaction term between type of surgery and time since surgery was not significant in any of the three models). The ef-

Table 2. Content and mean scores for QLQ-C30 and QLQ-BR23 areas

QLQ-C30	Mean(SD)	QLQ-BR23	Mean(SD)
Areas		Areas	
(1)Physical	88.2(15.1)	(1) body image	82.2(29.3)
(1)Role	86.5(24.5)	(1) sexual functioning	27.3(24.3)
(1)Emotional	76.7(25.6)	(1) sexual enjoyment	50.4(31.0)
(1)Cognitive	85.1(22.1)	(1) future perspective	65.2(33.8)
(1)Social	86.8(24.7)	(2) arm symptoms	18.9(23.2)
(1)Global	70.9(23.9)	(2) lymphoedema item	15.4(26.5)
(2)Fatigue	21.1(24.4)	(2) breast symptoms	14.8(18.2)
(2)Nausea	3.5(12.1)	(2) systemic therapy side effect	20.0(19.1)
(2)Pain	20.2(26.1)	(2) hot flashes	35.4(33.8)
(2)Dyspnoea	6.2(17.4)	(2) upset by hair loss	20.8(32.2)
(2)Sleep disturbance	31.3(32.6)		
(2)Appetite loss	7.5(18.2)		
(2)Constipation	17.9(29.2)		
(2)Diarrhoea	4.8(15.3)		
(2)Financial impact	12.9(29.3)		

(1) Functioning scales and/or items. Scores range from 0 to 100, where a higher score represents a higher functional level. (2) Symptoms scales and/or items. Scores range from 0 to 100, where a higher score represents a greater degree of symptoms.

fect of breast reconstruction on body image was then studied in mastectomized patients through univariate logistic regression analysis. No significant relationship was found between mastectomy with and without breast reconstruction and body image ($p=0.57$). Mastectomized patients without reconstruction had a slight tendency to have a higher risk of low body image OR=1.26 (95%CI: 0.42, 3.76).

With regard to the effect of time since surgery on QoL, univariate analysis identified three significant aspects: hot flashes (OR=0.84; 95%CI:0.84-0.93; $p<0.001$), breast symptoms (OR=0.88; 95%CI:0.80-0.97; $p=0.007$) and systemic side effects (OR=0.90; 95%CI:0.83-0.98; $p=0.012$). QoL was better in patients with more time since surgery. In all three cases, significance was maintained in the multivariate analysis (Table 4). Moreover, for the first two items, the effect of time since surgery was greater in patients who were mastectomized than in those who had conservative surgery, with p values for the interaction term between both variables equal to 0.041 for hot flashes and 0.039 for breast symptoms. No statistical significance was noted in cognitive functioning ($p=0.132$), sexual functioning ($p=0.068$), insomnia ($p=0.145$) and financial impact ($p=0.070$), with punctual estimates, suggesting better QoL in patients with more time since surgery in all areas except sexual functioning. Adjusted estimates maintained the magnitude of the OR and the non significant p values, but in any case they raised significant at $\alpha=0.05$ level (Table 4).

Discussion

Our main results are that QoL in a sample of Spanish long-term premenopausal breast cancer survivors was satisfactory, with moderate limita-

tions in emotional and sexuality dimensions, hot flashes and global QoL. The risk of low body image scores for patients subjected to mastectomy was 4-fold higher compared with patients with conservative surgery. Patients with a longer time since surgery had lower systemic side effects, hot flashes and breast symptoms. For the latter two, the time effect was more evident in patients who were mastectomized.

The demographic and clinical characteristics of the sample were representative of patients treated at the Hospital. QoL scores were generally satisfactory and in line with reference values provided by the EORTC QoL Group for QLQ-C30 in the general population [20]. Helgeson and Tomich [21] suggested that the QoL of long-term breast cancer survivors who remain disease-free after 5 years of follow-up may generally be comparable to that of healthy women of the same age.

Our scores were also in line with those from other studies of early-stage breast cancer survivors (with a shorter follow-up period) conducted with EORTC QoL instruments in premenopausal patients [14] and in patients with a wider age range (not only premenopausal) [3,5,9,22]. Some of the most prevalent symptoms in our study – sleep disturbance, hot-flashes – were in line with those in a review of studies of breast cancer survivors (with a variety of ages and stages) [2]. Unlike that review, we found no limitations in cognitive functioning or lymphoedema.

Limitations in the global QoL scale have appeared in other breast cancer studies by our group [16]. They have also appeared in other QoL studies with early-stage breast cancer survivors and a shorter follow-up period in the same age group [14] or with a wider variety of ages [22]. These lower scores in global QoL may be due to the fact that there were 7 answer categories for global

Table 3. Univariate and multivariate results for the effect of type of surgery (mastectomy vs conservative) on QoL

Quality of life areas (outcomes)	Quality of life	N (%)	Univariate		Multivariate [§]	
			Mastectomy - Conservative		Mastectomy - Conservative	
			OR (95% CI)	p value	OR _{Adj} (95%CI)	p value
Social functioning	Better functioning	181 (74.5)	2.58 (1.32,5.04)	0.005	1.68 (0.89,3.17)	0.124
	Lower functioning	62 (25.5)				
Body image	Better image	177 (72.8)	4.51 (2.30,8.83)	<0.001	4.28 (2.14,8.56)	<0.001
	Lower image	66 (27.2)				
Arm symptoms	Fewer symptoms	190 (78.2)	1.72 (0.85,3.49)	0.130	1.78 (0.86,3.71)	0.120
	More symptoms	53 (21.8)				

[§]Adjusted by age at diagnosis, marital status, limiting comorbidity and time since surgery

Table 4. Logistic univariate and multivariate results for time since surgery on QoL

Quality of life areas (outcomes)	Quality of life	N (%)	Univariate		Multivariate [§]		
			OR (95% CI)	p value	Patients	OR _{Adj} (95%CI)	p value
Hot flashes [#]	Fewer symptoms	163 (60.1)	0.84 (0.77, 0.93)	<0.001	Conservative	0.90 (0.81,1.01)	0.070
	More symptoms	80 (39.9)			Mastectomy		0.73 (0.59,0.89)
Breast symptom [#]	Fewer symptoms	172 (70.9)	0.88 (0.80,0.97)	0.007	Conservative	0.92 (0.83,1.03)	0.080
	More symptoms	81 (29.1)			Mastectomy		0.83 (0.69,1.00)
Systemic side effects	Fewer symptoms	159 (65.4)	0.90 (0.83,0.98)	0.012	All patients	0.90 (0.83,0.98)	0.008
	More symptoms	84 (34.6)					
Cognitive functioning	Better functioning	176 (72.4)	0.94 (0.86,1.02)	0.132	All patients	0.94 (0.86,1.02)	0.159
	Lower functioning	67 (27.6)					
Sexual functioning	Better functioning	61 (25.1)	1.09 (0.99,1.20)	0.068	All patients	1.10 (0.99,1.22)	0.079
	Lower functioning	183 (74.9)					
Insomnia	Fewer symptoms	100 (41.2)	0.95 (0.89,1.02)	0.145	All patients	0.96 (0.89,1.02)	0.229
	More symptoms	143 (58.8)					
Financial impact	Lower impact	189 (77.8)	0.91 (0.83,1.01)	0.070	All patients	0.90 (0.82,1.00)	0.068
	Higher impact	54 (22.2)					

[#]Interaction term ‘type of surgery* time since surgery’ significant in the multivariate analysis. Displayed OR obtained from the models stratified by type of surgery. [§]Adjusted by age at diagnosis, marital status, limiting comorbidity and type of surgery

QoL items rather than the 4 for the other scales. For global QoL items, patients thus had more higher-level categories to choose from (rather than just one on the other scales) and so were not obliged to choose the highest score.

Worries about future health are one of the main breast cancer QoL dimensions throughout the disease and follow-up process [16]. More precisely, fear of recurrence – a key component of future health worries – is a persistent stressor reported by breast cancer survivors [23]. In our study, mean future perspective limitations were moderate. This is important if we consider that patients were at the initial disease stages, had a good prognosis, and were in a long follow-up period, which could be expected to improve their perspective. These future perspective scores are in line with those of other studies involving early-stage breast cancer survivors with a shorter follow-up than ours and with the same [14] or wider age range [22].

Sexual limitations, one of the most frequent areas reported by breast cancer survivors, negatively impact QoL [24,25]. These limitations may have a multifactorial origin (physical, medical and psychological) [26]. The low sexual functioning scores in our sample are in line with those of early-stage breast cancer survivors from our cultural area – France [14] – and lower than in other cultural areas such as Germany [9] and Brazil [3]. We also found low sexual functioning in other breast cancer studies at our centre [27]. These regularly low sexuality scores among Spanish breast cancer patients suggest that cross-cultural differences in sexuality scores may be related to patients’ different criteria for evaluating their sexual functioning as adequate to their situation.

The limitations in insomnia are in line with those of a review of studies of breast cancer survivors [2] that suggested younger patients tend to have more insomnia. Our results indicating light limitations in fatigue are positive and in line with

those of other studies (with a variety of ages and stages and a shorter follow-up period) [2,28]. The systemic therapy side effects scale showed slight limitations, which suggest a low level of late toxicity related to chemotherapy and endocrine therapy. Moderate limitations occurred in hot flashes (mainly related to endocrine therapy). This result is adequate since hot flashes are a frequent symptom of breast cancer survivors that has been related to natural menopause and endocrine therapy [2]. It is advisable to ameliorate intense side effects of induced early menopause and fatigue as they could negatively affect patient QoL [2,29].

How treatments affect cognitive functioning in breast cancer survivors is a key area of research [2]. The EORTC QLQ-C30 cognitive functioning scale assesses concentration and memory – areas where limitations in breast cancer survivors may appear more often. As in Joly et al. study [14], which included premenopausal early-stage patients in follow-up, the cognitive functioning scale showed no clear limitations. As most patients had received chemotherapy, this suggests there is no clear and permanent negative effect of chemotherapy on the patient's brain. Future studies could assess whether cognitive impairment subsides after treatment [2] and whether factors such as a patient's young age enables the brain to better withstand treatment.

Differences between surgery-based groups were mainly found in body image and are in line with those of other studies of young [10] or various-age [5] early-stage breast cancer survivors with a shorter follow-up period. A study with more patients could help confirm the lack of differences in body image between the two mastectomy groups (one with and one without breast reconstruction). Arndt et al. [12] also found differences between surgery groups in early-stage breast cancer survivors (of various ages) in body image and social functioning 5 years after diagnosis and in a few more QoL areas than in our study (future perspective, sexual functioning and overall QoL) (Table 3).

We would like to stress these differences in body image since this important dimension has been related to other QoL areas (depression and overall QoL) in breast cancer survivors [30].

The arm symptoms scale showed only a marginal significance in the analysis of surgery-based groups. Moreover, both this scale and also the lymphoedema individual item showed low limitations in the whole sample. These results may be important since most patients (79%) were

subjected to lymphadenectomy. Lymphoedema is frequent in breast cancer survivors [2], and arm symptoms (including lymphoedema) have been significantly associated with poor QoL in early-stage breast cancer survivors (with a variety of ages and a shorter follow-up period) [31]. These results may indicate that surgery side effects were well managed and that patients adapted satisfactorily to their situation.

We found that time elapsed since surgery helped reduce treatment-related symptoms. We also found a statistically marginal effect in areas such as cognitive functioning and financial impact that should be further investigated. The trend towards lower sexual functioning in patients with more time since surgery may be related to several factors, including the ageing process. Our results are in line with those of other studies such as Tian et al. [5] (in early-stage breast cancer survivors with a variety of ages and a shorter follow-up period).

Future perspective showed no significant relationship with time after surgery. This is in line with a review of studies of cancer survivors in which fear of recurrence persists over a long follow-up period without significant changes [4]. This stability in future perspective and mean for this scale have been related to a possible persistence of some physical and psychological alterations that may sustain stress due to possible recurrence [23].

The problems faced by premenopausal early-stage patients even several years after diagnosis should be considered when providing interventions aimed at improving QoL [2]. These interventions could include a multidisciplinary treatment with psychological, social and medical interventions such as the one created by Bloom et al. [32].

Key points in this study are the patients' age, the cultural area, and the long follow-up period. However, the study could have benefited from a pre-treatment assessment of QoL in order to study changes and differences in QoL more accurately.

In conclusion, QoL in Spanish premenopausal early-stage breast cancer patients in a long follow-up period after surgery has been shown to be high, with moderate limitations in emotional and sexuality dimensions, hot flashes and global QoL. Differences between surgery-based groups were mainly in body image. A longer time since surgery reduces treatment side effects. These data may help patients to know which QoL levels to expect in the long follow-up period and professionals to improve the QoL of long-term premeno-

pausal breast cancer survivors.

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Conflict of interest

All authors declare that they have no conflict of interest.

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