

**Aim of the study:** Quality of life (QL) is important in premenopausal long-term breast cancer survivors. In this study we assessed QL and factors associated with future perspective and global QL in premenopausal early-stage long-term breast cancer survivors from Spain.

**Material and methods:** 243 premenopausal stage I-III relapse-free breast cancer patients who had received surgery 5–20 years previously completed EORTC QLQ-C30 and QLQ-BR23 questionnaires once during follow-up. Univariate and multivariate logistic regression analyses were performed.

**Results:** QL mean scores were high in most areas (> 80 in functioning; < 20 in symptoms). The main factors for future perspective were emotional and social functioning, fatigue, breast symptom, and body image. The main factors for global QL were fatigue, pain and physical functioning, and emotional and social functioning. The best logistic model to explain future perspective associated high emotional and social functioning and low breast symptoms with a lower risk of low future perspective ( $R^2 = 0.56$ ). Higher scores in physical and emotional functioning and lower scores in fatigue were associated with a lower risk of low global QL ( $R^2 = 0.50$ ).

**Conclusions:** Psychological, social, and physical factors were found to be possible determinants of global QL and future perspective. QL in premenopausal early-stage long-term breast cancer survivors may benefit from multidisciplinary treatment.

**Key words:** breast cancer; premenopausal, quality of life, survivors, determinants.

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# An evaluation study of the determinants of future perspective and global Quality of Life in Spanish long-term premenopausal early-stage breast cancer survivors

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## Introduction

The attention given to breast cancer in recent years has seen a shift from short-term to long-term patient's quality of life (QL) [1, 2]. Quality of life is considered especially important in long-term breast cancer survivors who were premenopausal at diagnosis [3]. Tumours in this population tend to be more aggressive, and patients are generally offered multi-modal therapies that can be more toxic than individual ones [4]. Their QL may be hampered by factors that are common among survivors, and also by specific problems such as transition to menopause. More research is required into the factors that determine the QL of these patients [3].

To our knowledge, few studies have assessed QL only in young early-stage breast cancer survivors [5] and none has been conducted in Spain. Moreover, most studies performed with breast cancer survivors (with different ages and disease stages) have a follow-up period of less than 10 years. More research is needed into long-term QL in breast cancer patients [6].

Worries about future health are considered one of the main QL dimensions in breast cancer [7]. Fear of recurrence, a key component of future health worries, is a common stress factor reported by breast cancer survivors [8]. Future perspective and overall QL have been compromised in a review of studies performed with premenopausal breast cancer survivors [3]. Few studies have analysed factors related to future perspective or global QL in young early-stage breast cancer survivors more than three years after diagnosis [9–11], and none of them has been conducted in our cultural area. These studies may allow health professionals to adjust follow-up management and interventions to the patients' needs [12].

Other studies of global QL [1, 12–20] and future perspective determinants [8, 13, 18, 20–26] have been conducted with breast cancer survivors in early or advanced disease stages and at a variety of ages.

Cross-cultural differences have been found in QL among breast cancer survivors [27]. QL studies conducted in different cultural areas may help to determine the characteristics of breast cancer survivors in each one.

The aims of this study were to assess QL in a sample of premenopausal early-stage breast cancer patients from Spain who are in a long period of follow-up and to evaluate the determinants of two key QL areas: future perspective and global QL. We expected the determinants of these QL

areas to be a combination of psychosocial and medical QL dimensions, such as emotional and social functioning, and fatigue. We also expected to find few clinical and demographic variables to be determinants of global QL and future perspective.

## Material and methods

### Participants

A consecutive sample of stage I–IIIA breast cancer patients treated at a tertiary metropolitan hospital in Spain was recruited (September 2011 – January 2014). Patients were premenopausal when treated and had undergone surgery 5 to 20 years previously. Premenopausal women were identified as those with menses and those without menses

**Table 1.** Sociodemographic and clinical characteristics of the sample

Characteristics	N	Percentage	Mean	SD
Present age (range 34–68)			54.2	6.8
Age when diagnosed (range 28–56)			44.7	5.3
Time since surgery (range 5–20 years)			9.8	4.0
Marital Status				
Single	31	12.8		
Married	177	72.8		
Widowed	12	4.9		
Separated	23	9.5		
Breast Surgery				
Conservative	164	67.5		
Mastectomy	79	32.5		
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	56	23.0		
Radiotherapy				
Yes	190	78.2		
No	40	21.8		
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		
Menopause				
Yes	206	84.8		
No	37	15.2		

LH-RH – luteinising hormone-releasing hormone

in the last six months but with plasmatic hormonal levels suggesting an active ovarian function. They were disease free, had no relapse or second malignancy, and may have received surgery and various adjuvant treatments. Patients with a second line of treatment or whose cognitive state did not permit QL evaluation were excluded.

### Measures

Patients completed the EORTC QLQ-C30 (3.0) [28] and the QLQ-BR23 [7] questionnaires, which had been translated into Spanish [29] and validated for use in Spain [30, 31]. The QLQ-C30 comprises 30 items that evaluate areas common to different tumour sites and treatments. It includes five functioning and eight symptoms scales and/or items, a financial impact item, and a global scale. The QLQ-BR23 evaluates areas associated with breast cancer and its treatments. It includes four functioning and four symptoms scales and/or items. Scores in all areas range from 0 to 100. A higher score represents a higher functional level or a higher degree of symptoms. Sociodemographic and clinical data were obtained from clinical records. QL questionnaires with < 70% of the items answered were excluded.

### Data collection procedures

Patients were addressed during one of their outpatient follow-up visits. They were given oral and written information about the research by their treating physician. Patients who provided informed consent completed the questionnaires once after their follow-up visit. This study followed the recommendations of the Declaration of Helsinki and was approved by the Ethics Committee of the Hospital.

### Statistical analysis

To identify which patients' characteristics were related to bad future perspective and low global QL (dependent variables), univariate logistic regression analyses were performed with the categorised scores as response variables and the sociodemographic, clinical (age at evaluation, age when diagnosed, marital status, breast and axillary surgery modalities, having/not having received chemotherapy, radiotherapy, and/or endocrine therapy, limiting comorbidity, menopause, time since surgery) and QL areas as explanatory (independent) variables (0–33 and 0–50 points were considered low future perspective and low global QL, respectively). Global QL was assessed through two specific QLQ-C30 items that assess overall health and overall QL, and future perspective through a QLQ-BR23 item that assesses worries about future health. Multivariate logistic regression models using the backward regression method and including those areas found to be significant in univariate logistic regression were also performed to complement the analyses. Calibration of the models was checked using the Hosmer & Lemenshow test, and the models were selected using statistical indicators such as the percentage of correct classification, the area under the ROC curve with its 95% CI, and the  $R^2$  of Nagelkerke.

## Results

Out of 259 candidates, 243 patients were evaluated. Reasons for not completing the questionnaires were administrative failure (10 cases) and patient refusal (6 cases). All questionnaires had > 70% of the items answered. The sociodemographic and clinical characteristics of these patients are shown in Table 1. The mean present age was 54.2 and the mean time since surgery was 9.8 years. Conservative surgery had been performed on 67.5% of the patients.

Quality of Life mean scores were high in most areas (> 80 points in functioning; < 20 points in symptoms areas; Table 2). Moderate limitations occurred in global QL, sleep disturbance, future perspective, and sexual functioning and enjoyment (affectation > 30). Light affectation (20 to 29 points) appeared in emotional functioning, fatigue, pain, and systemic therapy side effects.

### Future perspective

Mean future perspective was 65.2. No significant relationship was found between future perspective and any of the clinical and demographic variables in the univariate lo-

gistic regression analyses. The QL areas with the highest R<sup>2</sup> were emotional and social functioning, body image (higher values were associated with better future perspective), fatigue, arm symptoms, breast symptoms, and systemic therapy side effects (higher values were associated with lower future perspective) (Table 3).

The best logistic model to explain future perspective in the multivariate logistic regression analyses identified high emotional and social functioning and low breast symptoms (radiotherapy side effects) as variables associated with lower risk of low future perspective: R<sup>2</sup> = 0.56; ROC = 0.91 (95% CI: 0.86–0.95), and % of correct classification = 88%. Calibration of the model:  $\chi^2_7 = 5.25$  ( $p = 0.629$ ) (see Table 3).

### Global QL

Mean global QL was 70.9. A significant relationship was found between the risk of low global QL and comorbidity (OR = 3.96, 95% CI: 1.84–8.52, R<sup>2</sup> = 0.08) in the univariate logistic regression analyses. No other significant relationship was found between global QL and any of the clinical or demographic variables.

**Table 2.** Mean scores for QLQ-C30 and QLQ-BR23 areas and association with future perspective and global QL

QLQ-C30 AREAS	Mean (SD)	Bad Future Perspective			Low Global QL		
		OR (95% CI)	R <sup>2</sup>	P-value	OR (95% CI)	R <sup>2</sup>	P-value
Physical <sup>1</sup>	88.2 (15.1)	0.95 (0.93–0.97)	0.16	< 0.001	0.92 (0.89–0.94)	0.31	< 0.001
Role <sup>1</sup>	86.5 (24.5)	0.96 (0.94–0.97)	0.25	< 0.001	0.96 (0.95–0.98)	0.23	< 0.001
Emotional <sup>1</sup>	76.7 (25.6)	0.93 (0.91–0.95)	0.52	< 0.001	0.96 (0.94–0.97)	0.27	< 0.001
Cognitive <sup>1</sup>	85.1 (22.1)	0.96 (0.95–0.98)	0.20	< 0.001	0.96 (0.95–0.97)	0.20	< 0.001
Social <sup>1</sup>	86.8 (24.7)	0.96 (0.95–0.97)	0.26	< 0.001	0.96 (0.94–0.97)	0.27	< 0.001
Global <sup>1</sup>	70.9 (23.9)	0.95 (0.94–0.97)	0.29	< 0.001	–	–	–
Fatigue <sup>2</sup>	21.1 (24.4)	1.05 (1.03–1.06)	0.30	< 0.001	1.07 (1.05–1.09)	0.47	< 0.001
Nausea <sup>2</sup>	3.5 (12.1)	1.09 (1.05–1.24)	0.19	< 0.001	1.07 (1.03–1.10)	0.12	< 0.001
Pain <sup>2</sup>	20.2 (26.1)	1.04 (1.02–1.05)	0.25	< 0.001	1.05 (1.03–1.06)	0.31	< 0.001
Dyspnoea <sup>2</sup>	6.2 (17.4)	1.04 (1.02–1.06)	0.12	< 0.001	1.04 (1.02–1.06)	0.14	< 0.001
Sleep disturbance <sup>2</sup>	31.3 (32.6)	1.03 (1.02–1.04)	0.20	< 0.001	1.02 (1.01–1.04)	0.15	< 0.001
Appetite loss <sup>2</sup>	7.5 (18.2)	1.04 (1.02–1.05)	0.12	< 0.001	1.02 (1.01–1.04)	0.05	0.003
Constipation <sup>2</sup>	17.9 (29.2)	1.01 (0.99–1.02)	0.02	0.117	1.01 (1.00–1.02)	0.02	0.038
Diarrhoea <sup>2</sup>	4.8 (15.3)	1.02 (1.01–1.04)	0.04	0.012	1.02 (1.00–1.04)	0.02	0.053
Financial impact <sup>2</sup>	12.9 (29.3)	1.03 (1.02–1.04)	0.15	< 0.001	1.02 (1.01–1.03)	0.12	< 0.001
<b>QLQ-BR23 AREAS</b>							
Body image <sup>1</sup>	82.2 (29.3)	0.96 (0.95–0.98)	0.27	< 0.001	0.97 (0.96–0.99)	0.15	< 0.001
Sexual functioning <sup>1</sup>	27.3 (24.3)	0.98 (0.96–0.99)	0.07	0.002	0.98 (0.96–0.99)	0.07	< 0.001
Sexual enjoyment <sup>1</sup>	50.4 (31.0)	0.99 (0.98–1.01)	0.01	0.477	0.98 (0.97–0.99)	0.04	0.042
Future perspective <sup>1</sup>	65.2 (33.8)	–	–	–	0.97 (0.96–0.98)	0.22	< 0.001
Arm symptoms <sup>2</sup>	18.9 (23.2)	1.04 (1.03–1.06)	0.23	< 0.001	1.04 (1.02–1.05)	0.20	< 0.001
Breast symptoms <sup>2</sup>	14.8 (18.2)	1.06 (1.04–1.09)	0.29	< 0.001	1.04 (1.03–1.06)	0.16	< 0.001
Systemic therapy side effect <sup>2</sup>	20.0 (19.1)	1.06 (1.04–1.08)	0.27	< 0.001	1.06 (1.04–1.08)	0.25	< 0.001
Upset by hair loss <sup>2</sup>	20.8 (32.2)	1.02 (1.01–1.03)	0.11	0.006	1.02 (1.01–1.03)	0.10	0.008

<sup>1</sup>Functioning areas and global QL. The scores range from 0 to 100, where a higher score represents a higher functional level

<sup>2</sup>Symptoms areas and financial impact. The scores range from 0 to 100, where a higher score represents a greater degree of symptoms

**Table 3.** Multivariate analyses: predictive factors of future perspective and global QL

	Estimates		
	OR (95% CI)	P-value	R <sup>2</sup>
<b>Model 1: Risk to Low Future Perspective</b>			56%
Emotional <sup>1</sup>	0.94 (0.93–0.96)	< 0.001	
Social <sup>1</sup>	0.98 (0.97–1.00)	0.068	
Breast symptoms <sup>2</sup>	1.03 (1.01–1.06)	0.025	
<b>Model 2: Risk to Low Global QL</b>			50%
Physical <sup>1</sup>	0.97 (0.94–1.01)	0.135	
Emotional <sup>1</sup>	0.98 (0.97–1.00)	0.121	
Fatigue <sup>2</sup>	1.06 (1.03–1.08)	< 0.001	

<sup>1</sup>The scores range from 0 to 100, where a higher score represents a higher functional level

<sup>2</sup>The scores range from 0 to 100, where a higher score represents a greater degree of symptoms

The QL areas with the highest R<sup>2</sup> were physical, emotional, and social functioning (higher values were associated with higher global QL), and fatigue, pain, and systemic therapy side effects (higher values were associated with lower global QL; see Table 3).

The best logistic model to explain global QL in the multivariate logistic regression analyses showed that higher scores in physical and emotional functioning and lower scores in fatigue were associated with a lower risk of low global QL: R<sup>2</sup> = 0.50; ROC = 0.89 (95% CI: 0.84–0.93), and % of correct classification = 83%. Calibration of the model:  $\chi^2_8 = 12.36$  ( $p = 0.136$ ) (see Table 3).

## Discussion

The main results of this study are: QL mean scores in a sample of Spanish long-term premenopausal breast cancer survivors were high in most areas; the main QL factors related to future perspective were emotional and social functioning, fatigue, arm symptoms, breast symptoms, body image, and systemic therapy side effects; the main QL factors related to global QL were fatigue, pain, physical, emotional and social functioning, and systemic therapy side effects; two logistic models to identify which QL areas were most related with future perspective and global QL were fitted. Most clinical and biographical factors were not found to be determinants of future perspective or global QL.

QL scores were generally satisfactory. Our scores are similar to those found in other studies of early-stage breast cancer survivors with a shorter follow-up period that focused on premenopausal patients [5] or those with a wider age range [1, 24] and in which the EORTC instruments were administered. These scores are also in line with the EORTC reference values for the QLQ-C30 (general population) [32].

Future perspective limitations were moderate. This result is important if we take into account the fact that patients were at initial disease stages, had a good prognosis, and were in a long follow-up period, all of which may be expected to improve their perspective. These future perspective scores are in line with those from other studies of

early-stage breast cancer survivors (though with a wider age range and a shorter follow-up) [8].

Our results on QL determinants of global QL and future perspective are in line with those of other studies (with shorter follow-ups than ours) of young early-stage breast cancer survivors. These studies found emotional functioning to be an explanatory factor of future perspective [11] and physical and emotional functioning and body image (in our case with a lower R<sup>2</sup>) to be global QL explanatory factors [9, 10]. Like our study, another study of early-stage breast cancer patients at a variety of ages did not find body image to be a key determinant of global QL [19]. Our results are also in line with those of other studies of QL determinants of global QL [1, 12, 15, 16, 18, 19] and future perspective [8, 21, 23, 25, 26] conducted with breast cancer survivors (at early or advanced disease stages and a variety of ages, and a shorter follow-up period), which showed QL functioning and symptoms areas to be explanatory factors.

We found fatigue and social functioning to be key determinants of both future perspective and global QL. Fatigue has been considered a strong predictor of QL in breast cancer survivors [2, 33]. The QLQ-C30 social functioning scale assesses family life and social activities, which are considered key to supporting breast cancer survivors [1, 34]. This family and social support role is especially important in Spain [35].

We found a relationship between future perspective (which assesses worries about future health) and the arm symptoms scale, but not with the type of surgery administered. Liu *et al.* [8] found that surgical side effects (including arm symptoms) in early-stage breast cancer survivors (> 40 years old) were related to fear of recurrence (a key component of worries about future health) and considered the literature to be inconsistent regarding the impact of the type of surgery on fear of recurrence.

Our results on the clinical and demographic determinants of global QL and future perspective are in line with those of other studies of young early-stage breast cancer survivors (with shorter follow-ups than ours). Co-morbidity has been found to be a determinant of global QL [10], whereas age, adjuvant treatments, and, as we have already mentioned, type of surgery have not [9, 10]. Unlike us, Thewes *et al.* [11] found a relation between time since diagnosis and fear of recurrence. However, the fact that their study could include young early-stage patients with a shorter follow-up period (one year) may have influenced their results.

Other studies of early stage patients at a variety of ages found no relation between time since diagnosis and global QL or future perspective [14, 23, 24].

Co-morbidity has also been related to global QL in early-stage breast cancer survivors (at a variety of ages and with a shorter follow-up period) [16, 17]. Marital status has not been found to be a determinant of global QL or future perspective in studies of patients at early or a variety of stages and at a variety of ages (and with a shorter follow-up period) [8, 23].

Age has been found to be a determinant of global and future perspective in several studies conducted with

breast cancer survivors at initial and advanced stages [2, 8, 13, 14, 16, 20, 25, 26]. However, these results may have been influenced by the fact that the patients in all of these studies had a broader age range than ours. In other studies of patients at a variety of ages and initial disease stages, age was also not found to be a determinant of global QL or future perspective [13, 20]. In some studies, but not in others, adjuvant treatments and surgery modality have been shown to be determinants of global QL or future perspective in patients at early and advanced disease stages and at a variety of ages [8, 13, 14, 20, 23, 25, 26]. In all of the above studies, the follow-up period was shorter than in ours.

Areas measured by the QL questionnaires such as symptoms, side effects, and body image may be related to future perspective (worries about future health) because they could be reminders of the disease. It would be useful to study the level of knowledge women have of their cancer and whether they have a false interpretation of their symptoms and side effects as an indication of a possible negative evolution of their disease [36]. The presence of these chronic symptoms and side effects as possible reminders of the disease may also help to understand the lack of relationship between future perspective and time of follow-up: patients with no relapse and a longer follow-up period may be expected to have a better future perspective since they may believe their disease to be under control.

Some of the key points of this study are the patients' ages, the cultural area, and the long follow-up period. On the other hand, the study could have benefited from a longitudinal design in which QL was measured before treatment as well as during follow-up, in order to identify risk and the protective factors of QL more accurately.

In conclusion, psychological, social, and physical factors have been found to be possible determinants of future perspective and global QL in premenopausal long-term early-stage breast cancer survivors from Spain. These patients could benefit from a multidisciplinary treatment that could help to improve their QL.

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