

Quality of life trajectories during the first three years after diagnosis of breast cancer: the NEON-BC study

Luisa Lopes-Conceição, MSc DVM^{1,2}, Mariana Brandão, MD^{1,3}, Natália Araújo, PharmD MSc^{1,2}, Milton Severo, PhD^{1,2}, Teresa Dias, MD⁴, Bárbara Peleteiro, PhD^{1,2}, Filipa Fontes, PhD^{1,4}, Susana Pereira, PhD^{1,4}, Nuno Lunet, PhD^{1,2}.

¹EPIUnit—Instituto de Saúde Pública, Universidade do Porto, 4050-600 Porto, Portugal

²Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina da Universidade do Porto, 4200-319 Porto, Portugal

³Academic Promoting Team, Institut Jules Bordet, 1000 Brussels, Belgium

⁴Instituto Português de Oncologia do Porto, Rua Dr. António Bernardino de Almeida, 4200-075 Porto, Portugal

Address correspondence to Nuno Lunet, E-mail: nlunet@med.up.pt.

ABSTRACT

Background We aimed to identify and characterize quality of life trajectories up to 3 years after breast cancer diagnosis.

Methods A total of 460 patients were evaluated at baseline (before treatments), and after 1- and 3-years. Patient-reported outcomes, including quality of life (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, QLQ-C30), anxiety, depression and sleep quality, were assessed in all evaluations. Model-based clustering was used to identify quality of life trajectories.

Results We identified four trajectories without intersection during 3 years. The two trajectories characterized by better quality of life depicted relatively stable scores; in the other trajectories, quality of life worsened until 1 year, though in one of them the score at 3 years improved. Sociodemographic and clinical characteristics at baseline did not differ between trajectories, except for mastectomy, which was higher in the worst trajectory. Anxiety, depression and poor sleep quality increased from the best to the worst trajectory.

Conclusions The type of surgery and the variation of other patient-reported outcomes were associated with the course of quality of life over 3 years. More research to understand the heterogeneity of individual trajectories within these major patterns of variation is needed.

Keywords breast neoplasms, cluster analysis, patient-reported outcome measures, quality of life

Introduction

Breast cancer mortality is decreasing in most developed countries, despite increasing or stable incidence rates, and it is the most prevalent cancer 5 years after diagnosis, due to the frequent use of screening and more effective treatments.^{1,2}

The diversity and complexity of the problems resulting from the disease and its treatments could affect all domains of quality of life (QoL), including physical, emotional and social, at any time during treatment and remission periods. Women diagnosed with breast cancer may experience psychosocial distress (namely depression, anxiety, fear of recurrence and death and problems related to body image and feminine role) and physical symptoms (namely pain, fatigue and sleep disturbance).^{3,4} The improvement in breast cancer survival emphasizes the importance of assessing disability due to the disease or its treatment, as it impacts short- and long-term

QoL. Therefore, patient-reported outcomes (PRO) have become essential for evaluating the burden of cancer.⁵

Previous studies reported an association between sociodemographic, clinical and treatment characteristics and QoL in breast cancer patients, namely age, education, cancer stage, surgery and chemotherapy,^{6–8} however with inconsistent findings. Further, the effect of some factors on QoL

Luisa Lopes-Conceição, Research fellow

Mariana Brandão, Medical Doctor

Natália Araújo, Research fellow

Milton Severo, Researcher

Teresa Dias, Medical Doctor

Bárbara Peleteiro, Researcher

Filipa Fontes, Researcher

Susana Pereira, Medical Doctor

Nuno Lunet, Professor

may differ at different time points after diagnosis and during the course of survivorship. At diagnosis and before treatments, patients may experience psychosocial distress as anxiety, fear and disbelief and existential concerns regarding mortality.⁹ Depression and psychological problems related to body image, sexuality and femininity as well as cognitive disturbances and sleep disturbance are symptoms commonly referred by patients during treatments, and after their completion, most of them experience a mixture of elation, fear of recurrence and uncertainty.^{4,9,10} Some symptoms disappear or dissipate during the following years, or may be perceived as less important by the patients, whereas others develop gradually into long-term side effects.⁹

Changes in QoL over time in breast cancer patients have been reported previously. However, some studies examined only average changes in QoL, disregarding possible heterogeneity of this outcome among patients. Determining trajectory patterns of QoL in breast cancer patients and their associated characteristics may allow identifying patients at risk and providing patients with appropriate support throughout and following treatments. Previous studies^{11–13} on QoL trajectories focused specifically on the score of specific domains instead of the total score (e.g. physical, cognitive and social domains), used different questionnaires to assess QoL or missed a baseline evaluation before treatments' initiation.

The aim of this study was to describe the trajectories of QoL in a cohort of breast cancer patients during the first 3 years after diagnosis and to assess differences in sociodemographic and clinical characteristics among distinct trajectories of QoL and their association with other PRO.

Methods

The present study is based on a cohort study designed to estimate the incidence of neurological complications of breast cancer and its treatments (neuro-oncological complications of breast cancer—NEON-BC), as previously described in the detailed study protocol.¹⁴ Briefly, the cohort includes adult women consecutively admitted to the Breast Clinic of the Portuguese Institute of Oncology of Porto in 2012, with newly diagnosed breast cancer and proposed for surgery, either as primary treatment or after neoadjuvant chemotherapy. A total of 506 patients underwent a baseline evaluation before any cancer treatment, and 503 (99.4%) and 475 (93.9%) completed the 1- and 3-year evaluations, respectively (Fig. 1).

Participants evaluation

In the three evaluations, data on clinical characteristics and cancer treatments were obtained from medical records and

after a neurological evaluation and data on sociodemographic characteristics and PRO, including QoL, anxiety, depression and sleep quality, were self-reported.

The QoL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the Breast Cancer-specific Module QLQ-BR23.

The QLQ-C30 is a 30-item cancer-specific questionnaire of QoL composed of multi-item scales and single items that reflect the multidimensionality of the QoL construct. It incorporates five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, pain, and nausea and vomiting) and a global health status/QoL scale. Additionally, it incorporates six single items that evaluate other symptoms (including dyspnea, insomnia, appetite loss, constipation and diarrhea) and financial difficulties. The QLQ-BR23 incorporates multi-item scales to evaluate systemic therapy side effects, arm and breast symptoms, body image, sexual functioning and single items to assess sexual enjoyment, hair loss and future perspective.

In both QoL instruments, the items were answered on a four-point ordinal scale, from '1-not at all' to '4-very much', with the exception of the global health status/QoL scale of QLQ-C30, which has a seven-point response format, from '1-very poor' to '7-excellent'.^{15,16} All of the scales and single-item measures range in score from 0 to 100, with high scale score representing a higher response level. The scale scores are calculated using a linear transformation to standardize the average of the items that contribute to the scale. Thus, a high score for functional scale or for the global health status/QoL scale represents a high/healthy level of functioning or a high QoL, respectively, and the opposite is true for a symptom scale (a high score represents a high level of symptomatology/problems).¹⁷

Anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (HADS).¹⁸ The sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI).¹⁹

Statistical analysis

Patients with cancer stage IV at baseline ($n = 3$), cancer relapse until the 3-year evaluation ($n = 12$) and those with incomplete QLQ-C30 questionnaire in at least one of the three evaluations ($n = 9$) were excluded, and a total of 451 participants were considered for data analysis (Fig. 1).

Principal component analysis on the 30 items was used to evaluate the dimensionality of the items. The score of all items was reversed, except for items 29 and 30, and the final score of the questionnaire was the sum of individual scores of the 30 items and was expressed as α -scores, with higher scores indicating better QoL.

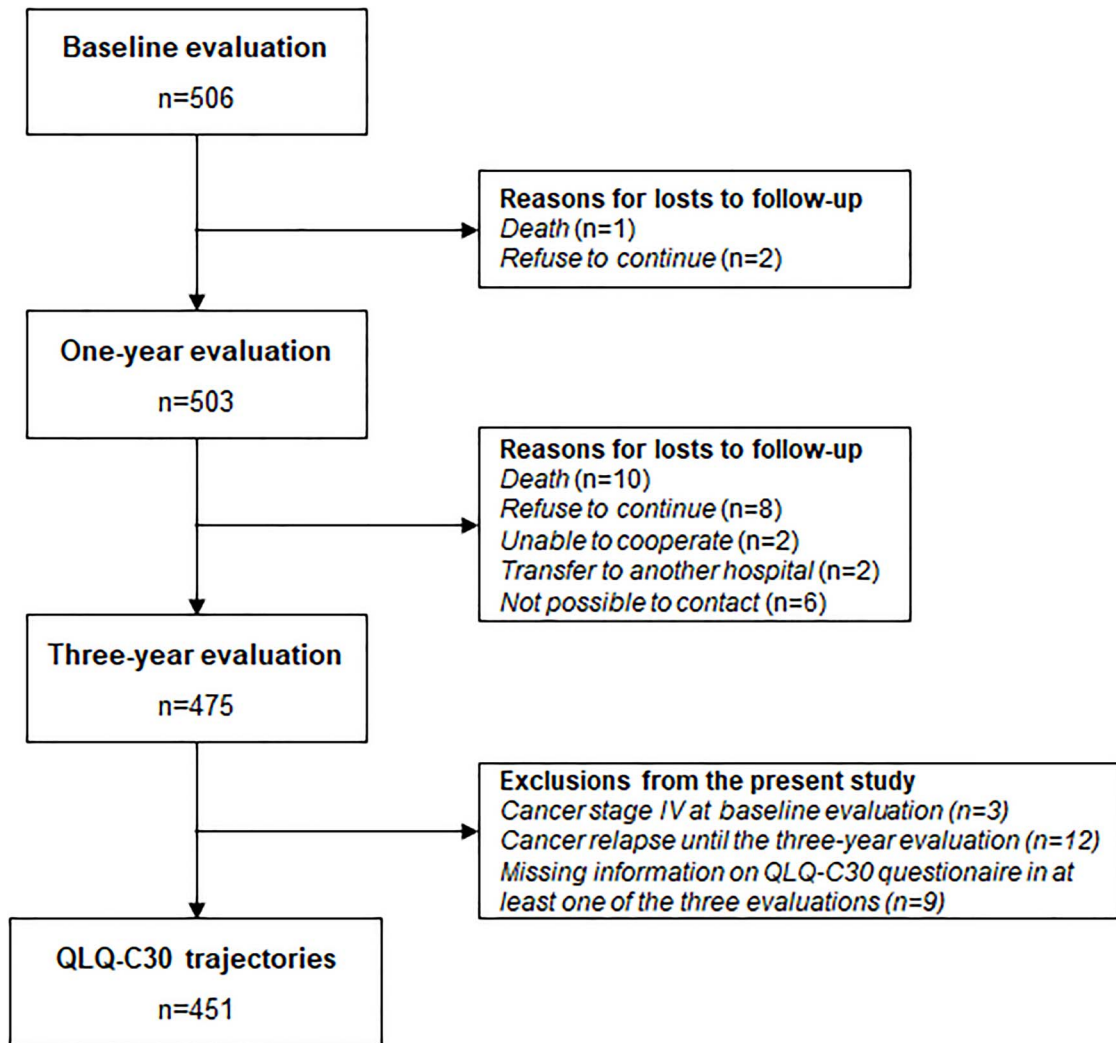


Fig. 1 Flowchart of participants included in the present study. n, number of patients; QLQ-C30, the Quality of Life Questionnaire Core 30 of the European Organization for Research and Treatment of Cancer.

Model-based clustering²⁰ was used to identify groups of patients with different patterns of variation in QLQ-C30 score, from the baseline to the 3-year evaluation. The model that allowed for the most homogeneous grouping of individual patterns of QoL was selected among those with the lowest Bayesian Information Criteria; thus, a four-component model was selected (Supplementary Material, Appendix A).

The QoL trajectories were defined to reflect the pattern of variation over the 3-year period, but were characterized regarding sociodemographic and clinical characteristics of the patients, as well as the scores obtained for other PRO (anxiety, depression and sleep quality) at each evaluation (baseline, 1-year and 3-year); data are presented as counts and proportions, for categorical variables, and means and standard deviations, for continuous variables. Univariate analysis was performed for comparisons within and between QoL trajectories, using

the chi-square test, for categorical variables, and analysis of variance (ANOVA), for continuous variables. ANOVA for repeated measures (for mean comparisons) or generalized estimating equations (for proportion comparisons) were used for comparison within each trajectory, and the Bonferroni correction was used for multiple pairwise comparisons.

Statistical analysis was conducted using Stata, version 11.2 (StataCorp, College Station, Texas, USA) and R, version 3.3.1 (R Core Team, Vienna, Austria).

Ethics

This study was approved by the Ethics Committee of the Portuguese Institute of Oncology of Porto (CES 406/011, CES 99/014 and CES 290/014). All the patients provided written informed consent.

Results

At baseline, the mean age of the participants was 55 years, and more than two thirds had up to 9 years of education. Most patients (55.4%) were diagnosed with cancer stage 0 and I, and 57.2% were postmenopausal. In addition to breast surgery, in the first year of follow-up, 83.8% received endocrine therapy, 73.8% were submitted to radiotherapy, 59.2% to chemotherapy and 12.9% received targeted therapy. Most patients (57.4%) initiated endocrine therapy during the first year and maintained the same drug until the third year and 26.3% changed drugs (Supplementary Material, Appendix B).

Figure 2 depicts the QoL trajectories. Four trajectories were identified: C1 ($n = 55$, 12.2%), C2 ($n = 171$, 37.9%), C3 ($n = 175$, 38.8%) and C4 ($n = 50$, 11.1%). The QLQ-C30 scores corresponded to gradually worse QoL from C1 to C4, without intersecion between the trajectories and with two major patterns being observed. C1 and C2 were characterized by better and relatively stable QoL, though in C1 there was a significant improvement between baseline and 1-year evaluations, followed by stable QoL until the 3-year evaluation, when the mean score was similar to the observed at baseline. In C2, the mean score did not change within the 3-year period. On the other hand, C3 and C4 presented worse QoL at baseline than C1 and C2, which worsened further in the first year. However, while in C3 the QoL did not change up to the 3-year evaluation, in C4 there was a significant improvement in the QoL, presenting a mean score at the third year similar to the observed at baseline.

The sociodemographic and clinical characteristics at baseline and breast cancer treatments performed during the first year of follow-up according to each trajectory are presented at Table 1. There were no statistically significant differences in these characteristics among the QoL trajectories, except for mastectomy, which was more frequent in C4.

The emotional functioning was the most affected domain during the 3 years and in the four trajectories, worsening from C1 to C4; however for C1 and C2 the worst point corresponded to the baseline evaluation, and for C4 corresponded to the 1-year evaluation. The other domains followed the same trend of deterioration from C1 to C4. The physical functioning worsened up to the 1-year evaluation, presenting at this point the worst mean scores in all trajectories, except in C1 that was characterized by stable scores during the 3 years. In C2 and C3, the role and social functioning varied inversingly in the 3-year period, since the former worsened and the latter improved. In the same period, the cognitive functioning also worsened in C1 and C2, presenting the worst mean scores at the 3-year evaluation, while in C3 and C4 this domain was more affected at 1 year. The mean scores in global health status/QoL scale are also worsening from C1 to C4, as

described for functional scales, and improved from baseline to 1-year evaluation in C1 and C2, while in the other trajectories the mean scores did not change during the 3 years (Table 2).

The body image, sexual functioning and future perspective decreased from C1 to C4, in baseline, 1-year and 3-year evaluations. In each trajectory, the body image decreased mainly from the baseline to the 1-year evaluation, except in C1 that did not present changes during the entire period. In C3, the sexual functioning decreased between baseline and 1-year evaluations, while in the remaining trajectories it did not change during the 3 years. Regarding future perspective, in all trajectories this outcome increased during the 3 years mainly between 1-year and 3-year evaluations (Table 2).

The proportion of patients with anxiety, depression and poor sleep quality increased from C1 to C4 over the period of 3 years after diagnosis. Anxiety was significantly more frequent at baseline than at 1-year in C2 and C3 and than at 3 years in all trajectories, except in C1 that did not present significant changes in the proportion of this outcome during the 3 years. Within each trajectory, there were no significant differences in the frequency of depression between the three evaluations, except for C4 that presented an increase from baseline to the 1-year follow-up and then a decrease between the 1- and the 3-year evaluations. Among each trajectory, the proportion of patients with poor sleep quality did not differ across the whole follow-up period, except in C3 that presented a lower prevalence at baseline than at the 1-year follow-up (Fig. 3).

Discussion

Main finding of this study

Four QoL trajectories were identified up to 3 years after diagnosis. These are characterized by differences in QoL at baseline and mostly by patterns of variation portraying either small variations or worsening until the first year, while returning to scores similar to those observed at baseline until the third year. The trajectories differed regarding the type of breast surgery and on the other evaluated PROs, namely anxiety, depression and sleep quality, which worsened gradually from C1 to C4.

What is already known on this topic

In the first 3 years after diagnosis, roughly half of patients presented good self-reported QoL (C1 and C2), more than one third presented moderate self-reported QoL (C3) and one tenth presented bad self-reported QoL (C4), comparing with reference values for breast cancer patients.²¹ Further, the best trajectories were characterized mainly by similar scores in functional scales of a general and a breast-cancer-specific questionnaires, except in sexual functioning and

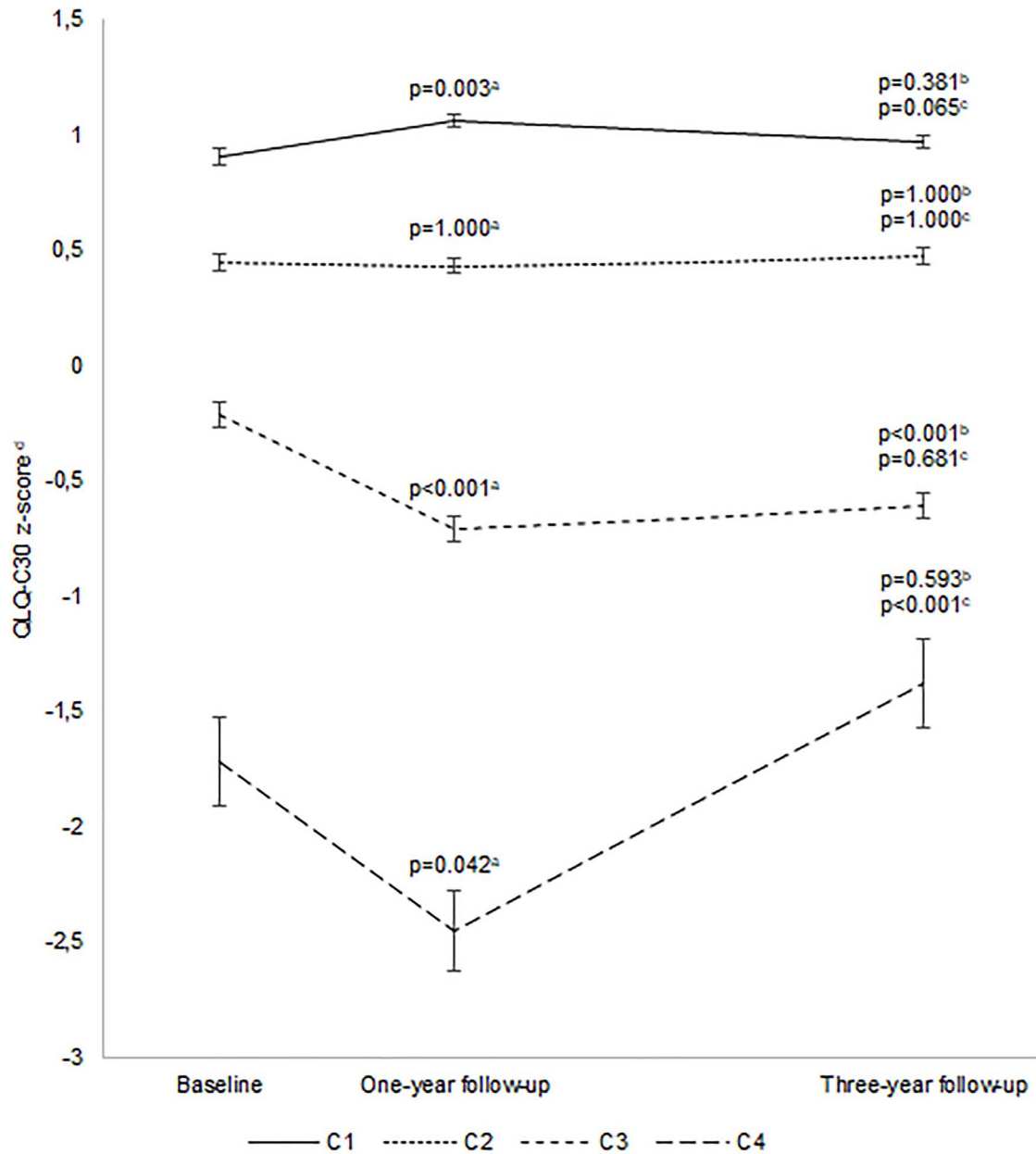


Fig. 2 Means and the corresponding 95% confidence intervals of the EORTC QLQ-C30, at baseline, 1-year and 3-year follow-up evaluations, for each trajectory identified (higher scores indicating better quality of life). EORTC QLQ-C30, the Quality of Life Questionnaire Core 30 of the European Organization for Research and Treatment of Cancer. ^aP-value for the comparison between baseline and 1-year evaluations; ^bP-value for the comparison between baseline and 3-year evaluations; ^cP-value for the comparison between 1- and 3-year evaluations; ^dQLQ-C30 scores were obtained from principal component analysis and confirmatory factor analysis (Supplementary Material, Appendix C) and are expressed as z-scores, with higher scores indicating better quality of life.

future perspective, considered good in C1 and moderate in C2, taking into account the reference values.²¹ The other two trajectories are quite different. In C3, the functional scales varied from good (e.g. social functioning) to bad (e.g. emotional functioning), while in C4 the functional scales were mainly bad. Similar patterns were observed for the variation of other PRO. At baseline, the prevalence of anxiety was lower or similar (C1, C2 and C3) and higher (C4) than that reported in

previous studies,²² and at 3-year evaluation, only C4 presented a prevalence of anxiety higher than that expected for long-term survivors.²³ Furthermore, in C1 and C2, the prevalence of depression was none or negligible, respectively, while in the other two trajectories, the prevalence could be considered similar to higher, compared to a pooled prevalence of depression of 20% (95% CI = 16–24%) previously reported.²⁴ Additionally, the prevalence of poor sleep quality of nearly

Table 1 Sociodemographic and clinical characteristics at baseline and breast cancer treatments performed during the first 3 years of follow-up, according to each trajectory identified.

EORTC QLQ-C30 ^a					
	C1 n = 55	C2 n = 171	C3 n = 175	C4 n = 50	P-value
Age (years), mean (SD)	53.7 (10.4)	55.4 (11.2)	55.6 (10.3)	54.5 (10.8)	0.640
Education (years), n (%)					0.540
≤4	25 (45.5)	70 (40.9)	80 (45.7)	18 (36.0)	
5–9	17 (30.9)	45 (26.3)	52 (29.7)	14 (28.0)	
≥10	13 (23.6)	56 (32.7)	43 (24.6)	18 (36.0)	
Cancer stage ^b , n (%)					0.629
0	3 (5.5)	10 (5.8)	16 (9.1)	2 (4.0)	
I	30 (54.5)	81 (47.4)	83 (47.4)	25 (50.0)	
II	14 (25.5)	60 (35.1)	47 (26.9)	17 (34.0)	
III	8 (14.5)	20 (11.7)	29 (16.6)	6 (12.0)	
Menopausal status ^c , n (%)					0.796
Premenopausal	27 (49.1)	72 (42.1)	73 (41.7)	21 (42.0)	
Postmenopausal	28 (50.9)	99 (57.9)	102 (58.3)	29 (58.0)	
Lymphedema, n (%)					0.144
At 1 year	2 (3.6)	14 (8.2)	14 (8.0)	8 (16.0)	
At 3 years	4 (7.3)	20 (11.7)	33 (18.9)	9 (18.0)	0.089
Breast surgery, n (%)					
Surgery type					
Breast-conserving	37 (67.3)	87 (50.9)	92 (52.6)	16 (32.0)	0.004
Mastectomy	18 (32.7)	84 (49.1)	83 (47.4)	34 (68.0)	
Axillary surgery					
None/SLNB	41 (74.5)	112 (65.5)	119 (68.0)	32 (64.0)	0.604
ALND	14 (25.5)	59 (34.5)	56 (32.0)	18 (36.0)	
Chemotherapy, n (%)	35 (63.6)	104 (60.8)	99 (56.6)	29 (58.0)	0.762
Radiotherapy, n (%)	47 (85.5)	124 (72.5)	131 (74.9)	31 (62.0)	0.052
Endocrine therapy, n (%)	45 (81.8)	147 (86.0)	144 (82.3)	43 (86.0)	0.748
Targeted therapy (Trastuzumab), n (%)	7 (12.7)	27 (15.8)	20 (11.4)	4 (8.0)	0.430

Bold values denote statistical significance at the p-value < 0.05 level.

ALND, axillary lymph node dissection; EORTC QLQ-C30, the Quality of Life Questionnaire Core 30 of the European Organization for Research and Treatment of Cancer; n, number of patients; SD, standard deviation; SLNB, sentinel lymph node biopsy.

^aQLQ-C30 trajectories only used data from 451 patients, due to missing data.

^bCancer stage was classified according to the 7th edition of the American Joint Committee on Cancer Staging Manual.

^cWhen menopausal status was not specified, all women with at least 60 years, women who underwent a bilateral oophorectomy and those with an intact uterus and being amenorrheic for 12 or more consecutive months prior to the diagnosis in the absence of alternative pathological or physiological cause and follicle stimulating hormone and serum estradiol levels within the laboratory's reference ranges were classified as postmenopausal, or otherwise as premenopausal.³⁶

25% (C1) and 50% (C2) is in accordance with a pooled prevalence of sleep disturbances of 40% (95% CI = 29–52%) reported previously.²⁵ However, in the other trajectories, the prevalence of this outcome was higher.

The patterns observed in our study are compatible with the fact that the initial stages of treatment and the months following its completion may be physically and emotionally demanding, resulting in decreased QoL. Most women with

breast cancer experience moderate to high levels of anxiety before treatment, due to hopelessness, uncertainty, loss of control and a decrease in life satisfaction.²⁶ The period following treatment completion is a transitional time of considerable psychosocial distress, during which most women experience a mixture of happiness, fear and uncertainty.²⁷ In our study, anxiety at baseline was higher than at 1 year in the two more prevalent trajectories and than at 3 years in all trajectories,

Table 2 Mean scores of functional scales of EORTC QLQ-C30 and EORTC QLQ-BR23 and global health status/QoL scale of EORTC QLQ-C30 at baseline, 1-year and 3-year follow-up evaluations, according to each trajectory identified (higher scores indicating high level of functioning or a high quality of life).

<i>Evaluation</i>		<i>C1</i> <i>n = 55</i>	<i>C2</i> <i>n = 171</i>	<i>C3</i> <i>n = 175</i>	<i>C4</i> <i>n = 50</i>
<i>EORTC QLQ-C30</i>					
Physical functioning, mean (SD)					
	Baseline	96.6 (7.1)	93.2 (8.7) ^a	85.9 (13.7) ^{a,b}	73.1 (20.6) ^a
	1-year	96.5 (4.9)	90.3 (9.2) ^a	75.0 (16.4) ^{a,c}	63.2 (17.7) ^{a,c}
	3-year	97.6 (4.7)	92.0 (9.5)	79.8 (14.6) ^{b,c}	73.5 (18.0) ^c
	<i>P-value</i> ^d	0.547	0.013	<0.001	0.010
Role functioning, mean (SD)					
	Baseline	100.0 (0.0)	96.8 (8.5) ^{a,b}	90.5 (15.7) ^{a,b}	63.0 (33.0)
	1-year	98.2 (6.9)	93.6 (11.8) ^{a,c}	79.8 (21.2) ^{a,c}	52.0 (28.7)
	3-year	97.9 (5.6)	87.9 (16.2) ^{b,c}	71.0 (22.8) ^{b,c}	59.3 (26.1)
	<i>P-value</i> ^d	0.068	<0.001	<0.001	0.167
Emotional functioning, mean (SD)					
	Baseline	83.8 (13.6) ^{a,b}	75.5 (16.8) ^{a,b}	61.4 (21.5)	35.7 (25.0) ^b
	1-year	93.5 (8.6) ^a	80.2 (15.4) ^a	59.5 (20.8)	27.2 (23.9) ^c
	3-year	90.8 (9.0) ^b	80.9 (17.2) ^b	63.1 (21.2)	50.7 (28.3) ^{b,c}
	<i>P-value</i> ^d	<0.001	0.004	0.279	<0.001
Cognitive functioning, mean (SD)					
	Baseline	95.5 (8.8) ^b	89.1 (14.3) ^b	79.6 (19.5) ^{a,b}	58.3 (23.6) ^a
	1-year	94.5 (9.1) ^c	87.8 (12.4) ^c	70.8 (22.3) ^a	45.7 (28.5) ^{a,c}
	3-year	90.6 (11.0) ^{b,c}	83.4 (16.5) ^{b,c}	70.5 (24.1) ^b	56.7 (26.3) ^c
	<i>P-value</i> ^d	0.022	<0.001	<0.001	0.035
Social functioning, mean (SD)					
	Baseline	97.6 (7.5)	92.7 (13.7) ^b	87.7 (17.9)	71.3 (31.1)
	1-year	99.1 (5.0)	94.9 (10.4) ^c	83.5 (20.1) ^c	64.0 (28.6)
	3-year	99.4 (3.1)	98.1 (6.7) ^{b,c}	88.0 (18.0) ^c	78.0 (25.1)
	<i>P-value</i> ^d	0.181	<0.001	0.044	0.051
Global score, mean (SD)					
	Baseline	79.1 (18.1) ^a	67.1 (19.0) ^{a,b}	58.0 (17.9)	48.0 (21.9)
	1-year	89.4 (9.7) ^{a,c}	71.5 (15.6) ^a	58.4 (17.6)	46.7 (20.8)
	3-year	82.4 (14.1) ^c	71.9 (15.0) ^b	56.8 (14.8)	53.5 (19.2)
	<i>P-value</i> ^d	<0.001	0.013	0.644	0.218
<i>EORTC QLQ-BR23</i>					
Body image, mean (SD)					
	Baseline	98.3 (5.2)	97.2 (6.2) ^a	91.7 (15.2) ^{a,b}	87.8 (22.3) ^{a,b}
	1-year	96.7 (10.2)	89.7 (16.7) ^{a,c}	84.0 (24.2) ^a	61.0 (36.1) ^a
	3-year	97.3 (10.0)	95.4 (10.7) ^c	86.8 (21.0) ^b	72.8 (32.8) ^b
	<i>P-value</i> ^d	0.603	<0.001	0.002	<0.001
Sexual functioning, mean (SD)					
	Baseline	24.2 (23.5)	19.7 (22.0)	18.5 (20.3) ^a	19.0 (22.6)
	1-year	28.5 (27.7)	20.3 (22.3)	13.3 (18.5) ^a	11.0 (14.9)
	3-year	22.7 (23.4)	20.5 (21.6)	16.1 (18.3)	13.0 (15.9)
	<i>P-value</i> ^d	0.458	0.943	0.042	0.075

Continue

Table 2 Continued

Evaluation		C1 n = 55	C2 n = 171	C3 n = 175	C4 n = 50
EORTC QLQ-BR23					
Future perspective, mean (SD)					
Baseline		61.2 (29.9) ^{a, b}	46.2 (30.9) ^b	37.1 (29.9) ^b	15.3 (24.5) ^b
1-year		74.5 (24.0) ^{a, c}	50.7 (34.6) ^c	37.7 (30.9) ^c	27.3 (33.5) ^c
3-year		85.5 (24.6) ^{b, c}	82.7 (25.9) ^{b, c}	68.8 (34.3) ^{b, c}	66.0 (37.2) ^{b, c}
P-value ^d		<0.001	<0.001	<0.001	<0.001

Bold values denote statistical significance at the p-value < 0.05 level.

The higher values indicate higher level of functioning and quality of life (the values vary between 0 and 100). At each evaluation (baseline, 1-year and 3-year follow-up), there are statistically significant differences among the four trajectories presented in the table (P-value < 0.001). EORTC QLQ-C30, the Quality of Life Questionnaire Core 30 of the European Organization for Research and Treatment of Cancer; EORTC QLQ-BR23, the breast cancer-specific module of the European Organization for Research and Treatment of Cancer; n, number of patients; SD, standard deviation.

^aThere are statistically significant differences between the baseline and the 1-year follow-up evaluation within the same trajectory.

^bThere are statistically significant differences between the baseline and the 3-year follow-up evaluation within the same trajectory.

^cThere are statistically significant differences between the 1-year and the 3-year follow-up evaluation within the same trajectory.

^dP-value for the comparison among the three evaluations (baseline, 1-year and 3-year follow-up) within each trajectory.

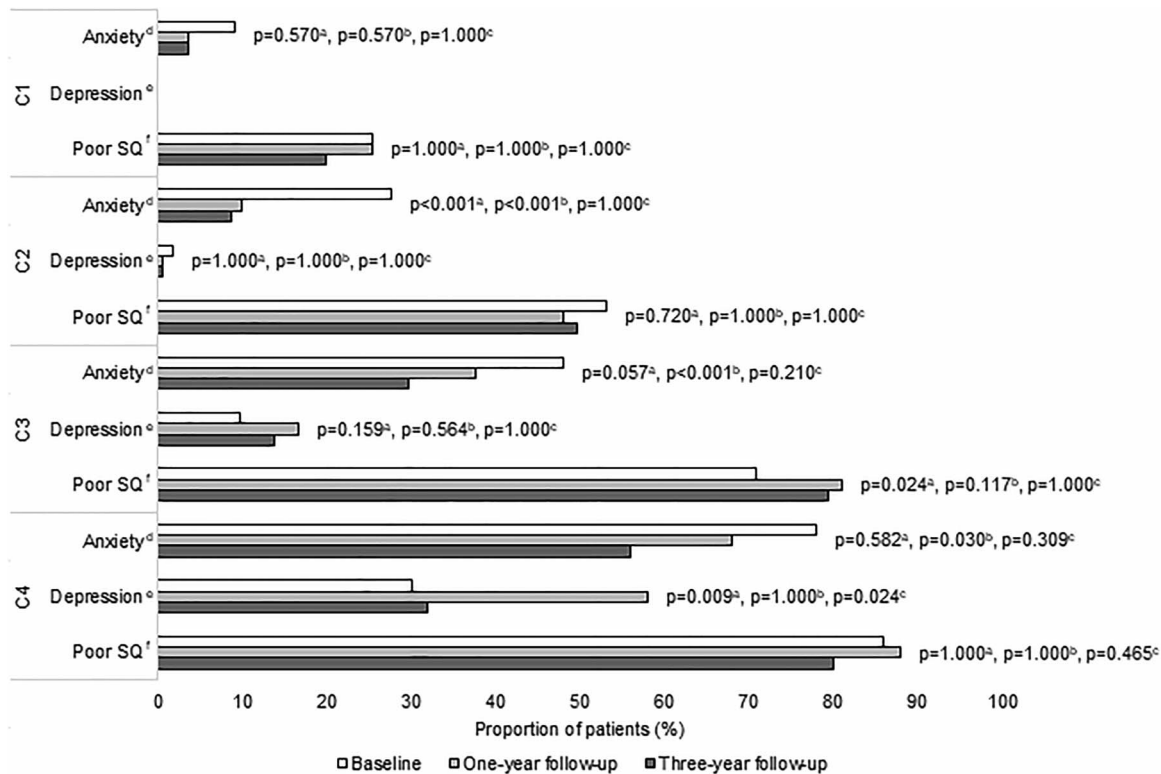


Fig. 3 Proportion of patients with anxiety, depression and poor sleep quality at baseline, 1-year and 3-year follow-up evaluations, according to each trajectory identified. EORTC QLQ-C30 SQ, sleep quality. ^aP-value for the comparison between baseline and 1-year evaluations; ^bP-value for the comparison between baseline and 3-year evaluations; ^cP-value for the comparison between 1- and 3-year evaluations; anxiety ^dand depression ^ewere defined whenever a score greater than or equal to 11 in anxiety or depression subscale of the Hospital Anxiety and Depression Scale, respectively, was obtained; ^fpoor sleep quality was defined whenever a score greater than five in the Pittsburgh Sleep Quality Index was obtained.

except in the best trajectory that did not change during the 3 years.

Women submitted to mastectomy are more likely to present depression, which may reflect the disfiguring nature of surgery that can also lead to other psychological problems related to body image, sexuality and femininity.^{28,29} A more favorable impact on QoL has been described for breast-conserving surgery.¹⁰ In our study, there was a higher proportion of women submitted to mastectomy in trajectories with poor self-reported QoL. Further, the body image decreased mainly between baseline and 1-year in most patients, but, in each time point, was mainly worse in trajectories with poor self-reported QoL; the sexual functioning was mainly stable during the 3 years in most patients and mainly worse in trajectories with poor self-reported QoL.

The psychological distress experienced by breast cancer patients, related to anxiety and depression, is associated with impaired QoL especially emotional, social and cognitive functioning.³⁰ In our study, the emotional functioning, involving feelings of tension, irritation, depression or worry, was the most reported affected domain during the 3 years and in all trajectories, which may be explained by the challenges that women have to deal with from diagnosis and during the course of their survivorship.

Most patients presented a worsening pattern in physical functioning during the first year, presenting at this point the worst mean scores. Fatigue, hot flashes, pain, cognitive impairment and lymphedema are common symptoms associated with breast cancer treatments, and, consequently, to a worse self-reported physical functioning observed 1 year after diagnosis.^{27,31} Further, in breast cancer patients the cognitive disfunction is usually associated with treatments, namely chemotherapy and hormone therapy, and with fatigue, anxiety and depression, and decreased QoL.³¹ These factors may explain the deteriorating trend in cognitive functioning during the 3 years, in the best trajectories, or mainly during the first year, in the worst trajectories.

Psychological distress associated to traumatic events such as cancer diagnosis may also contribute to poor sleep quality.³² It is associated with a wide range of detrimental psychological and physiological effects, namely fatigue, mood disturbances, impaired memory and concentration.³³ In the present study, poor sleep quality was more frequent in the trajectories of poorer QoL, and only C3 presented changes during the 3 years, with an increase in this outcome in the first year.

By their nature of being reported by the patient, the PRO cannot be separated from the characteristics inherent to the individual. Personality characteristics and coping strategies adopted by patients have been reported as predictors of self-

reported QoL. Optimism and the use of active and engagement coping strategies have been associated with better QoL, while pessimism and disengagement and avoidance strategies have been associated with worse QoL and higher levels of anxiety and depression.^{12,34} Therefore, patients' personality and coping strategies adopted by them may explain the worsening gradient observed in all PRO, from C1 to C4. However, the absence of data regarding these variables during the study period did not allow us to test this hypothesis in our sample.

Previous studies reported an association between sociodemographic and clinical characteristics and QoL in breast cancer patients; however, the findings were not consistent across studies.⁸ It has been suggested that the younger patients may have to deal with work aspirations, child care and plans for the future and, consequently, are not prepared for health problems³⁵; on the other hand, older age predicted poorer QoL regarding physical and role functioning, associated with other comorbidities.⁸ Further, some studies found an association between higher education level and better QoL, while others found no association.⁸ Also, some studies reported that advanced cancer stage predicted poorer QoL, while others found no association.⁸ Nevertheless, in the present study these variables did not differ between the four trajectories.

What this study adds

To the best of our knowledge, this is the first study determining QoL trajectories in breast cancer patients using the total scores of a general QoL questionnaire (EORTC QLQ-C30), based on baseline evaluations conducted before treatment onset. In previous studies,^{11–13} the first evaluation occurred after the treatments' initiation and QoL trajectories were defined for the score of specific domains instead of the total score^{11–13} or using different instruments to assess QoL.^{11,13} One study evaluated patients almost 18 years older, on average, than those included in the present investigation. Also the duration of follow-up differed across the mentioned studies: 18 months after baseline evaluation (within 8 months of diagnosis),¹³ 55 months post-diagnosis¹¹ and 7 years.¹² Despite these methodological differences, and the fact that distinct trajectories were identified in each study, most women reported consistently medium or high QoL, or experienced recovery over time within each of the domains.^{11–13}

The major strengths of the present study are the use of a large prospective cohort design, with a long-term and nearly complete follow-up, and the evaluation of QoL prior to any breast cancer treatment. Additionally, QoL was assessed comprehensively and could be related with other PRO.

Limitations of this study

Some study limitations need to be mentioned. The first evaluation was performed soon after breast cancer diagnosis, which could have negatively influenced the self-reported QoL at baseline. This may have contributed for an underestimation of the variation in the QoL scores between the baseline and the first year of follow-up, though the proportion of patients who reported worse QoL as a consequence of the traumatic event of the cancer diagnosis is unknown. Also, the generalizability of the findings is limited to patients submitted to breast cancer surgery and with cancer stage between 0 and III, taking into account that patients presenting cancer stage IV or relapse during the study period were excluded from the present study because of the small sample size. Additionally, some trajectories were observed in a small number of patients, and the estimates in these groups lack precision; larger samples are needed for a more robust characterization of these groups. Finally, QoL is a subjective and a broad concept, not directly observable, that depends on person's views and experiences. Its measurement is challenging, but difficulties on its assessment could be partially overcome with the application of a widely used instrument, such as QLQ-C30.

Conclusions

Our study showed that nearly half of women presented moderate or bad QoL prior to treatments which persisted during 3 years. The type of surgery and the variation of other PRO, namely anxiety, depression and sleep quality, were associated with the course of QoL. Sociodemographic and clinical characteristics at baseline were not different between the trajectories. These findings highlight the importance of monitoring QoL during the course of survivorship, and reinforce the necessity of management of other patient-reported outcomes, namely anxiety, depression and sleep quality, to improve QoL both in the short- and long-term. More research to understand the heterogeneity of individual trajectories within these major patterns of variation is needed.

Supplementary data

Supplementary data are available at the *Journal of Public Health* online.

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Conflicts of interest

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References

- 1 Ferlay J, Soerjomataram I, Ervik M, Dikshit R *et al.* *GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: LARC CancerBase No. 11* [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. <http://globocan.iarc.fr> (05 January 2018, date last accessed).
- 2 Amaro J, Severo M, Vilela S *et al.* Patterns of breast cancer mortality trends in Europe. *Breast (Edinburgh, Scotland)* 2013;**22**: 244–53.
- 3 Ganz PA. Psychological and social aspects of breast cancer. *Oncology (Williston Park)* 2008;**22**:642–6 (50; discussion 50, 53).
- 4 Syrowatka A, Motulsky A, Kurteva S *et al.* Predictors of distress in female breast cancer survivors: a systematic review. *Breast Cancer Res Treat* 2017;**165**:229–45.
- 5 Lipscomb J, Gotay CC, Snyder CF. Patient-reported outcomes in cancer: a review of recent research and policy initiatives. *CA Cancer J Clin* 2007;**57**:278–300.
- 6 Engel J, Kerr J, Schlesinger-Raab A *et al.* Predictors of quality of life of breast cancer patients. *Acta Oncol* 2003;**42**:710–8.
- 7 Engel J, Kerr J, Schlesinger-Raab A *et al.* Quality of life following breast-conserving therapy or mastectomy: results of a 5-year prospective study. *Breast J* 2004;**10**:223–31.

- 8 Brandao T, Schulz MS, Matos PM. Psychological adjustment after breast cancer: a systematic review of longitudinal studies. *Psycho-Oncology* 2017;**26**:917–26.
- 9 Institute of Medicine (US) and National Research Council (US) National Cancer Policy Board; Hewitt M, Herdman R, Holland J (eds). *Meeting Psychosocial Needs of Women with Breast Cancer*, Psychosocial Needs of Women with Breast Cancer, Vol. 3, Washington, DC: National Academies Press, 2004. <https://www.ncbi.nlm.nih.gov/books/NBK215940/>. (24 July 2019, date last accessed).
- 10 Akca M, Ata A, Nayir E *et al.* Impact of surgery type on quality of life in breast cancer patients. *J Breast Health* 2014;**10**:222–8.
- 11 Helgeson VS, Snyder P, Seltman H. Psychological and physical adjustment to breast cancer over 4 years: identifying distinct trajectories of change. *Health Psychol* 2004;**23**:3–15.
- 12 Dura-Ferrandis E, Mandelblatt JS, Clapp J *et al.* Personality, coping, and social support as predictors of long-term quality-of-life trajectories in older breast cancer survivors: CALGB protocol 369901 (alliance). *Psycho-Oncology* Nov 2017; **26**(11):1914–1921.
- 13 Goyal NG, Levine BJ, Van Zee KJ *et al.* Trajectories of quality of life following breast cancer diagnosis. *Breast Cancer Res Treat* 2018;**169**:163–73.
- 14 Pereira S, Fontes F, Sonin T *et al.* Neurological complications of breast cancer: study protocol of a prospective cohort study. *BMJ Open* 2014;**4**:e006301.
- 15 Aaronson NK, Ahmedzai S, Bergman B *et al.* The European Organization for Research and Treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;**85**:365–76.
- 16 Sprangers MA, Groenvold M, Arraras JI *et al.* The European Organization for Research and Treatment of cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *J Clin Oncol* 1996;**14**:2756–68.
- 17 Fayers PM, Aaronson NK, Bjordal K *et al.* *EORTC QLQ-C30 Scoring Manual*. European Organisation for Research and Treatment of Cancer, 2001.
- 18 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361–70.
- 19 Buysse DJ, Reynolds CF 3rd, Monk TH *et al.* The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;**28**:193–213.
- 20 Fraley C, Raftery AE. Model-based clustering, discriminant analysis, and density estimation. *J Am Stat Assoc* 2002;**97**:611–31.
- 21 Scott NW, Fayers P, Aaronson NK *et al.* *EORTC QLQ-C30 Reference Values Manual*. EORTC Quality of Life Group, 2008.
- 22 Linden W, Vodermaier A, Mackenzie R, Greig D. Anxiety and depression after cancer diagnosis: prevalence rates by cancer type, gender, and age. *J Affect Disord* 2012;**141**:343–51.
- 23 Maass SW, Roorde C, Berendsen AJ *et al.* The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: a systematic review. *Maturitas* 2015;**82**:100–8.
- 24 Krebber AM, Buffart LM, Kleijn G *et al.* Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. *Psycho-Oncology* 2014;**23**:121–30.
- 25 Leysen L, Lahousse A, Nijs J *et al.* Prevalence and risk factors of sleep disturbances in breast cancer survivors: systematic review and meta-analyses. 2019. *Support Care Cancer* 2019 Dec; **27**(12): 4401–4433.
- 26 Gold M, Dunn LB, Phoenix B *et al.* Co-occurrence of anxiety and depressive symptoms following breast cancer surgery and its impact on quality of life. *Eur J Oncol Nurs* 2016;**20**:97–105.
- 27 Paraskevi T. Quality of life outcomes in patients with breast cancer. *Oncol Rev* 2012;**6**:e2.
- 28 Kaminska M, Kubiatowski T, Ciszewski T *et al.* Evaluation of symptoms of anxiety and depression in women with breast cancer after breast amputation or conservation treated with adjuvant chemotherapy. *Ann Agric Environ Med* 2015;**22**:185–9.
- 29 Al-Ghazal SK, Fallowfield L, Blamey RW. Comparison of psychological aspects and patient satisfaction following breast conserving surgery, simple mastectomy and breast reconstruction. *Eur J Cancer (Oxford, England: 1990)* 2000;**36**:1938–43.
- 30 Montazeri A. Health-related quality of life in breast cancer patients: a bibliographic review of the literature from 1974 to 2007. *J Exp Clin Cancer Res: CR* 2008;**27**:32.
- 31 Pinto AC, de Azambuja E. Improving quality of life after breast cancer: dealing with symptoms. *Maturitas* 2011;**70**: 343–8.
- 32 Ancoli-Israel S. Sleep disturbances in cancer: a review. *Sleep Med Res* 2015;**6**:45–9.
- 33 Fiorentino L, Ancoli-Israel S. Insomnia and its treatment in women with breast cancer. *Sleep Med Rev* 2006;**10**:419–29.
- 34 Kvillemo P, Branstrom R. Coping with breast cancer: a meta-analysis. *PLoS One* 2014;**9**:e112733.
- 35 Mosher CE, Danoff-Burg SA. Review of age differences in psychological adjustment to breast cancer. *J Psychosoc Oncol* 2005;**23**: 101–14.
- 36 De Vos FY, van Laarhoven HW, Laven JS *et al.* Menopausal status and adjuvant hormonal therapy for breast cancer patients: a practical guideline. *Crit Rev Oncol Hematol* 2012;**84**:252–60.