THERAPEUTIC ADVANCES in
Medical Oncology

Original Research

Evaluating changes in the breast cancer-related quality of life of young women with breast cancer: long-term results from a multicenter prospective cohort

Bryan F. Vaca-Cartagena, Fernanda Mesa-Chavez, Ana S. Ferrigno Guajardo, Hatem A. Azim Jr, Federico Rotolo, Alejandra Platas, Alan Fonseca, Marlid Cruz-Ramos, Ana Rodriguez, Alejandro Mohar and Cynthia Villarreal-Garza

Abstract

Background: Young women with breast cancer (YWBC) typically undergo intensive treatment that negatively impacts their quality of life (QoL). However, limited information is available on how their QoL changes, as most research has focused on older patients.

Objectives: To assess changes in QoL among YWBC, identify the most affected QoL domains, and identify the factors associated with these changes.

Design: Joven & Fuerte is a multicenter cohort of women aged ⩽40 in Mexico with newly diagnosed BC from 2014 to 2020.

Methods: Participants completed the European Organization for Research and Treatment of Cancer Breast Cancer module QLQ-BR23 questionnaire at five different time points from enrollment until year 5 postdiagnosis. Clinical and treatment data were also collected. Group-based multivariate trajectory modeling was used to analyze longitudinal changes across QoL domains and classify patients into appropriate groups. Logistic models were then employed to identify associations between variables and group classification.

Results: A total of 477 women (median age: 36 years; interquartile range 32–38) were included. Most had public health insurance (87%) and were diagnosed with stage II (49%) or III (39%) BC. Two trajectory groups, namely, "good" and "poor," were identified based on QLQ-BR23 scores. Most patients ($n = 294$, 62%) were in the poor group. In the good group, sexual enjoyment scores remained stable from baseline to year 5 (51.4), whereas those in the poor group decreased (51.0–37.3). Distress related to hair loss over time declined, with scores decreasing from 36.3 to 27.0 in the good trajectory group and from 43.4 to 31.2 in the poor trajectory group. For future perspective, the good group improved from 56.4 to 79.0, while the poor group increased from 39.3 to 57.2. Patients with human epidermal growth factor receptor 2-positive BC (adjusted odds ratio (aOR) = 0.57, 95% confidence interval (CI) 0.35–0.94, $p = 0.028$) and those with public health insurance (aOR = 0.41, 95% CI 0.16–0.90, $p = 0.035$) were less likely to belong to the poor trajectory group.

Conclusion: A high proportion of YWBC experience a poor QoL trajectory over time, particularly in areas related to sexual health, future perspective, and hair loss.

Keywords: breast neoplasms, EORTC QLQ-BR23, quality of life, sexuality, young women with breast cancer

Received: 15 November 2024; revised manuscript accepted: 8 April 2025.

Ther Adv Med Oncol

2025, Vol. 17: 1–16

DOI: 10.1177/17588359251337493

Correspondence to:
Cynthia Villarreal-Garza
Breast Cancer Center, Hospital Zambrano Hellion TecSalud, Tecnologico de Monterrey, Batallón de San Patricio 112, Real San Agustín, 66260 San Pedro Garza García, Mexico

Médicos e Investigadores en la Lucha contra el Cáncer de Mama, Ciudad de México, Mexico
cynthia.villarreal@tecsalud.mx

Bryan F. Vaca-Cartagena
Breast Cancer Center, Hospital Zambrano Hellion TecSalud, Tecnologico de Monterrey, San Pedro Garza García, Mexico

Division of Pulmonary, Allergy, and Sleep Medicine, Mayo Clinic, Jacksonville, FL, USA

Fernanda Mesa-Chavez
Hatem A. Azim Jr
Breast Cancer Center, Hospital Zambrano Hellion TecSalud, Tecnologico de Monterrey, San Pedro Garza García, Mexico

Ana S. Ferrigno Guajardo
Department of Medicine, Yale University School of Medicine, New Haven, CT, USA

Federico Rotolo
Biomarkers Statistics, Sanofi, Montpellier, France

Alejandra Platas
Departamento de Investigacion y de Tumores Mamarios, Instituto Nacional de Cancerologia, Ciudad de México, Mexico

Médicos e Investigadores en la Lucha contra el Cáncer de Mama, Ciudad de México, Mexico

Alan Fonseca
Departamento de Investigacion y de Tumores Mamarios, Instituto Nacional de Cancerologia, Ciudad de México, Mexico

Marlid Cruz-Ramos
Investigadora por México del Consejo Nacional de Humanidades, Ciencias y Tecnologías (CONAHCYT), Instituto Nacional de Cancerologia, Ciudad de México, Mexico

Ana Rodriguez
Médicos e Investigadores en la Lucha contra el Cáncer de Mama, Ciudad de México, Mexico

Alejandro Mohar
Unidad de Investigación Biomédica en Cáncer, Instituto Nacional de Cancerología e Instituto de Investigaciones Biomédicas, UNAM, Ciudad de México, Mexico

Introduction

Breast cancer (BC) is the most frequently diagnosed malignancy and the leading cause of cancer-related death among women aged ⩽40 years.[1] In the United States, the average annual percent change in the incidence of BC from 2012 to 2021 was twofold higher in younger women than in older women (i.e., those aged >40 years; 1.4% vs 0.7%, respectively).[2] Notably, in Latin America, the incidence of BC in young women (20%) is much higher than that in developed countries (12%),[3,4] making it a major public health concern in the region.

Young women with breast cancer (YWBC) often present at an advanced stage, and the frequency of aggressive tumor subtypes is high, leading to poor survival outcomes and the need for intensive treatments.[5,6] Although anticancer therapies improve survival rates, patients who receive these treatments experience acute and long-term side effects.[7,8] Among YWBC, some of the most concerning side effects are those related to body image, sexual health, fertility, and menopause.[9] Furthermore, some adverse events can persist long after treatment, affecting career, employment, and family-specific goals, and substantially deteriorating the quality of life (QoL) of YWBC.[10]

Research has shown that YWBC experience more depressive symptoms, fatigue, and worse cognitive and sexual function than healthy age-matched controls and older patients do.[11,12] While the most significant decline in QoL occurs during active treatment phases,[10,13,14] recovery to baseline levels often takes longer in YWBC than in older patients. Even after 10 years of treatment, the QoL has been reported to remain lower than that in the general population.[14]

Although YWBC may share common characteristics and age-specific goals as a group, research studies involving older patients have shown that within a studied population, certain subgroups experience a greater decline in QoL.[15–20] Given this heterogeneity, our study aimed to evaluate longitudinal changes in QoL among YWBC, identify the specific domains and subgroups at higher risk of deterioration, and explore the sociodemographic, clinical, and treatment factors associated with these outcomes.

Methods

This study included data collected from the Joven & Fuerte cohort, a multicenter, prospective cohort involving three cancer referral centers in Mexico, in which women aged ⩽40 years who had been recently diagnosed with BC between 2014 and 2020 were enrolled.[21] To assess changes in the QoL over time, we administered QoL questionnaires at several points throughout the patient's journey. The questionnaires were applied at the time of diagnosis, 6 months after diagnosis, and 1 year after, when patients were actively undergoing treatment. Questionnaires were also administered during the survival phase to assess medium-term changes (2–3 years after diagnosis) and long-term changes (4–5 years after diagnosis) in the QoL. During the survival phase, patients were under surveillance or received endocrine therapy, depending on their molecular subtype. At the same time, clinical and treatment data were gathered from the patients' medical records. Patient responses, clinical and treatment data were collected and managed via REDCap electronic data capture tools hosted at Instituto Tecnológico y de Estudios Superiores de Monterrey.[22,23] The study protocol received approval from the Research Ethics Committees at the Instituto Nacional de Cancerología (#OM CM-J 03) and the School of Medicine at Instituto Tecnológico y de Estudios Superiores de Monterrey. Participants provided study consent before joining the study. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology "STROBE" statement (Supplemental File).[24]

QoL instrument

The patients in the Joven & Fuerte cohort were asked to complete the European Organization for Research and Treatment of Cancer Breast Cancer module (EORTC QLQ-BR23) at the abovementioned time points. The QLQ-BR23 is a BC-specific instrument consisting of 23 questions, including multi-item scales and single-item measures, all of which are rated on a 4-point Likert scale.[25] This questionnaire evaluates four functional scales/items (i.e., body image, future perspective, sexual functioning, and sexual enjoyment) and four symptom scales/items (i.e., systemic therapy side effects, upset by hair loss, arm symptoms, and breast symptoms). As per the QLQ-BR23 manual,[26] raw scores were calculated and then transformed linearly to obtain overall scores ranging from 0 to 100 for each scale/item. Higher scores on the functional scales indicate better functioning, whereas higher scores on symptom scales reflect more severe symptoms.

Study population

This study included patients between 18 and 40 years with stages 0–III BC who completed the QLQ-BR23 questionnaire at least once over the 5-year period. The analysis in this study focused on data collected from patients before disease recurrence or the diagnosis of a second primary malignancy. Patients with metastatic disease were excluded from the present analysis because they experience more significant psychological consequences of advanced disease,[27] and the objectives of therapy in that population are different from the curative intent in patients with early-stage disease.

Statistical analysis

Group-based multivariate trajectory modeling was used to analyze changes in the QoL of YWBC over the 5 years following their diagnoses. This statistical method models individual-level heterogeneity in trajectories of longitudinally measured variables by assuming that there are meaningful subgroups within the population being studied and identifies clusters of patients with similar QoL trajectories over time.[28] Patients are grouped based on various scales or items related to the outcome of interest (i.e., QoL in the present study), and the shape of the trajectory is defined by a polynomial regression of time.[29,30] This approach allowed us to use all eight scales of the QLQ-BR23 questionnaire to identify the trajectory groups.

To determine the appropriate number of groups, we tested models with one to four trajectory groups and employed a third-degree polynomial, which we deemed appropriate to model complex patterns within our data. We used four criteria to determine the final number of groups: (i) low values of information criteria (Akaike-, Bayesian-, consistent Akaike-, sample size-adjusted Bayesian-, Hannan-Quinn information criteria); (ii) whether the average posterior probability of assignment was at least 70%; and (iii) whether each trajectory comprised at least 10% of the total study sample.

Group-based multivariate trajectory modeling employs an expectation-maximization algorithm for maximum likelihood estimation, which can handle missing values under the missing at random assumption.[28,30] Briefly, the algorithm alternates between imputing missing data based on their conditional expectation given observed data and current parameter estimates and updating parameters through maximum likelihood estimation.[30] To address potential local maxima, the algorithm is run multiple times with different random initial values, and the solution with the highest likelihood is included.[30]

Describing the population

The sociodemographic, clinical, and treatment characteristics of the groups were summarized via descriptive statistics. Medians and interquartile ranges (IQR) were used for continuous variables, and numbers and percentages for categorical variables. Comparisons among groups in terms of these variables were with Chi-square, Fisher's exact test, and Kruskal–Wallis test.

Predictors of trajectory group classification

In addition, the relationships between variables of interest (e.g., sociodemographic, clinical, and treatment characteristics) and trajectory group classification were explored via binary logistic regression. Variables with a p-value <0.1 in a univariable regression model were included in a multivariable regression model. Multicollinearity among variables was assessed using the variance inflation factor (VIF). If the VIF exceeded 5, only one variable from the pair was retained in the final model. The group with the best scores was selected as the reference, as we were particularly interested in understanding which variables were associated with poor outcomes. Owing to the exploratory nature of this analysis, no adjustment for multiplicity was undertaken. All analyses were conducted via R Statistical Software version 4.2.2 and the GBMT package for trajectory analysis.[30,31] Statistical significance was defined as a two-tailed $p < 0.05$.

Results

The Joven & Fuerte cohort included 590 young women. For this analysis, we excluded patients with de novo metastatic BC, those who did not complete any QLQ-BR23 questionnaires, and those who only completed questionnaires after disease recurrence (Supplemental Figure 1). Thus, a total of 477 women, with a median age of 36 years (IQR 32–38), were enrolled in the study. To determine the optimal number of groups, we tested models with one to four trajectories and found that for each model, each group had an average posterior probability greater than 70%.

However, we discarded models with three or four groups because the sample size in some trajectories fell below our defined criteria (i.e., 10%). Among the remaining two models, the one with the lowest average rank was the one with two groups (1.8) compared with the one with only one group (4.0). Therefore, we selected the model with two groups because it provided the best fit and met clinically important criteria; we subsequently labeled these groups "good" and "poor" based on their functional and symptom scale scores. The model selection metrics are shown in Supplemental Table 1.

Most patients ($n = 294$, 62%) were assigned to the poor trajectory group, whereas the remaining patients ($n = 183$, 38%) were placed in the good trajectory group (Table 1). Both groups had similar sociodemographic, clinical, and treatment characteristics at inclusion. Although not statistically significant, the poor trajectory group had a numerically greater percentage of individuals in a partnership ($n = 189$ (64%) vs $n = 107$ (58%)), had an educational background of high school or higher ($n = 140$ (48%) vs $n = 83$ (45%)), had private insurance ($n = 26$ (9%) vs $n = 8$ (4%)), and received a greater percentage of anthracycline-containing regimens ($n = 246$ (84%) vs $n = 144$ (79%)) than did the good trajectory group, respectively.

Functional scales

With respect to body image, the good trajectory group maintained a relatively stable trend over time, starting with high baseline scores of 92.8 and showing only slight variations during follow-up: 90.2 at 1 year, 90.9 at 2 years, and 89.7 at year 5, as illustrated in Figure 1. By contrast, the poor trajectory group exhibited greater fluctuations, with baseline scores of 75.4 decreasing to 65.3 at 15 months and 64.7 at year 5.

For sexual functioning, both groups followed a similar pattern. The good group began with baseline values of 29.3, which increased to 35.9 at 30 months but then declined to 27.8 by year 5. Similarly, the poor group experienced fluctuations, starting at 30.6 and decreasing to 25.6 by year 5.

In terms of sexual enjoyment, the good group remained stable, with a mean score of 51.4 throughout the covered period. There was more variability in the poor group, with scores decreasing from 51.0 at baseline to 44.4 in the first year, and then improving to 53.4 by month 42 before ultimately dropping below baseline again to 37.3 at year 5.

Regarding future perspectives, both groups demonstrated notable improvements over time. The good trajectory group showed improvements from a baseline score of 56.4–79.0 at year 5, while the poor trajectory group, while also showing improvements, had lower overall values, starting at 39.3 and increasing to 57.2 by the end of the study.

Symptom scales

The trajectories for the symptom scale scores of the two groups are shown in Figure 2. In terms of systemic therapy side effects, a relatively stable trend over time was maintained in both groups. In the good group, initial values were 16.4 and 16.7 at 6 months, followed by continuous improvement through year 5, when the score was below the baseline value (14.3). Similarly, in the poor group, there was a slight increase from baseline (25.7) to month 8 (27.7), and by year 5, the scores remained slightly higher than the initial values (27.9).

With respect to breast symptoms, the good group started with scores of 16.9, which steadily improved to 10.4 by the end of the follow-up. The poor group also showed consistent improvement, but with higher values at each time point, with initial scores of 27.3 decreasing to 14.9 by year 5.

Regarding arm symptoms, the good trajectory group had stable scores over time, starting with a baseline value of 8.2, slightly worsening to 10.9 by 30 months, and then improving to 7.1 by year 5. Similarly, the poor group began with higher baseline scores of 17.6. Then, there was a slight deterioration to 20.6 at 1 year, followed by fluctuations over time, and a score of 20.1 was ultimately achieved at year 5.

With respect to hair loss, both groups showed significant improvement from baseline to year 5. In the good group, the scores improved from 36.3 to 27.0, whereas in the poor group, the scores improved from 43.4 to 31.2 by the end of the follow-up. Supplemental Tables 2–9 present the mean scores for each group across the functional

Table 1. Sociodemographic and clinical characteristics according to QoL trajectory groups.

Variable	Overall ($n = 477$, 100%)	Good group ($n = 183$, 38%)	Poor group ($n = 294$, 62%)	p Value
Age				
Median ($Q1$, $Q3$)	36.0 (32.0, 38.0)	36.0 (33.0, 38.0)	36.0 (32.0, 38.0)	0.449
Education level				
>High school	223 (47%)	83 (45%)	140 (48%)	0.528
⩽High school	237 (50%)	95 (52%)	142 (48%)	
Missing	17 (4%)	5 (3%)	12 (4%)	
Marital status				
Not partnered	164 (34%)	71 (39%)	93 (32%)	0.132
Partnered	296 (62%)	107 (58%)	189 (64%)	
Missing	17 (4%)	5 (3%)	12 (4%)	
Number of children				
Median ($Q1$, $Q3$)	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	0.802
Missing	18 (4%)	5 (3%)	13 (4%)	
Employment status				
Unemployed	287 (60%)	119 (65%)	168 (57%)	0.117
Employed	173 (36%)	59 (32%)	114 (39%)	
Missing	17 (4%)	5 (3%)	12 (4%)	
Monthly household income (MXN $)				
<6800	279 (58%)	110 (60%)	169 (57%)	0.695
⩾6800	152 (32%)	57 (31%)	95 (32%)	
Missing	46 (10%)	16 (9%)	30 (10%)	
Type of insurance				
Private insurance	34 (7%)	8 (4%)	26 (9%)	0.056
Public insurance	416 (87%)	167 (91%)	249 (85%)	
Missing	27 (6%)	8 (4%)	19 (6%)	
Regular exercise				
No	243 (51%)	90 (49%)	153 (52%)	0.394
Yes	200 (42%)	82 (45%)	118 (40%)	
Missing	34 (7%)	11 (6%)	23 (8%)	

(Continued)

Table 1. (Continued)

Variable	Overall (*n* = 477, 100%)	Good group (*n* = 183, 38%)	Poor group (*n* = 294, 62%)	*p* Value
Regular smoking				
No	339 (71%)	132 (72%)	207 (70%)	0.824
Yes	106 (22%)	40 (22%)	66 (22%)	
Missing	32 (7%)	11 (6%)	21 (7%)	
Regular alcohol consumption				
No	318 (67%)	127 (69%)	191 (65%)	0.378
Yes	127 (27%)	45 (25%)	82 (28%)	
Missing	32 (7%)	11 (6%)	21 (7%)	
Body mass index category				
Overweight or obese	280 (59%)	112 (61%)	168 (57%)	0.437
Underweight or normal	192 (40%)	70 (38%)	122 (41%)	
Missing	5 (1%)	1 (1%)	4 (1%)	
Stage				
0	11 (2%)	2 (1%)	9 (3%)	0.456
I	47 (10%)	20 (11%)	27 (9%)	
II	233 (49%)	93 (51%)	140 (48%)	
III	186 (39%)	68 (37%)	118 (40%)	
Subtype				
HR−HER2+	33 (7%)	14 (8%)	19 (6%)	0.198
HR+HER2−	250 (52%)	87 (48%)	163 (55%)	
HR+HER2+	70 (15%)	34 (19%)	36 (12%)	
TNBC	124 (26%)	48 (26%)	76 (26%)	
Breast surgery				
Mastectomy	354 (74%)	133 (73%)	221 (75%)	0.321
Breast-conserving surgery	114 (24%)	46 (25%)	68 (23%)	
None	6 (1%)	4 (2%)	2 (1%)	
Missing	3 (1%)	0 (0%)	3 (1%)	

(Continued)

Table 1. (Continued)

Variable	Overall (*n* = 477, 100%)	Good group (*n* = 183, 38%)	Poor group (*n* = 294, 62%)	*p* Value
Axillary surgery				
Axillary dissection	283 (59%)	110 (60%)	173 (59%)	0.569
Sentinel node biopsy	184 (39%)	69 (38%)	115 (39%)	
None	7 (1%)	4 (2%)	3 (1%)	
Missing	3 (1%)	0 (0%)	3 (1%)	
Chemotherapy schemes				
Anthracycline-based	390 (82%)	144 (79%)	246 (84%)	0.099
No chemotherapy	53 (11%)	21 (11%)	32 (11%)	
Non-containing anthracycline	30 (6%)	17 (9%)	13 (4%)	
Missing	4 (1%)	1 (1%)	3 (1%)	
Chemotherapy timing				
Neoadjuvant chemotherapy	240 (50%)	97 (53%)	143 (49%)	0.589
Adjuvant chemotherapy	180 (38%)	64 (35%)	116 (39%)	
No chemotherapy	53 (11%)	21 (11%)	32 (11%)	
Missing	4 (1%)	1 (1%)	3 (1%)	
Hormone therapy schemes				
Tamoxifen and/or aromatase inhibitors	199 (42%)	82 (45%)	117 (40%)	0.551
Containing LHRHa	105 (22%)	37 (20%)	68 (23%)	
No hormone therapy	169 (35%)	63 (34%)	106 (36%)	
Missing	4 (1%)	1 (1%)	3 (1%)	
Radiotherapy				
No	129 (27%)	53 (29%)	76 (26%)	0.475
Yes	344 (72%)	129 (70%)	215 (73%)	
Missing	4 (1%)	1 (1%)	3 (1%)	

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LHRHa, luteinizing hormone-releasing hormone analog; MXN $, Mexican peso; QoL, quality of life; TNBC, triple-negative breast cancer.

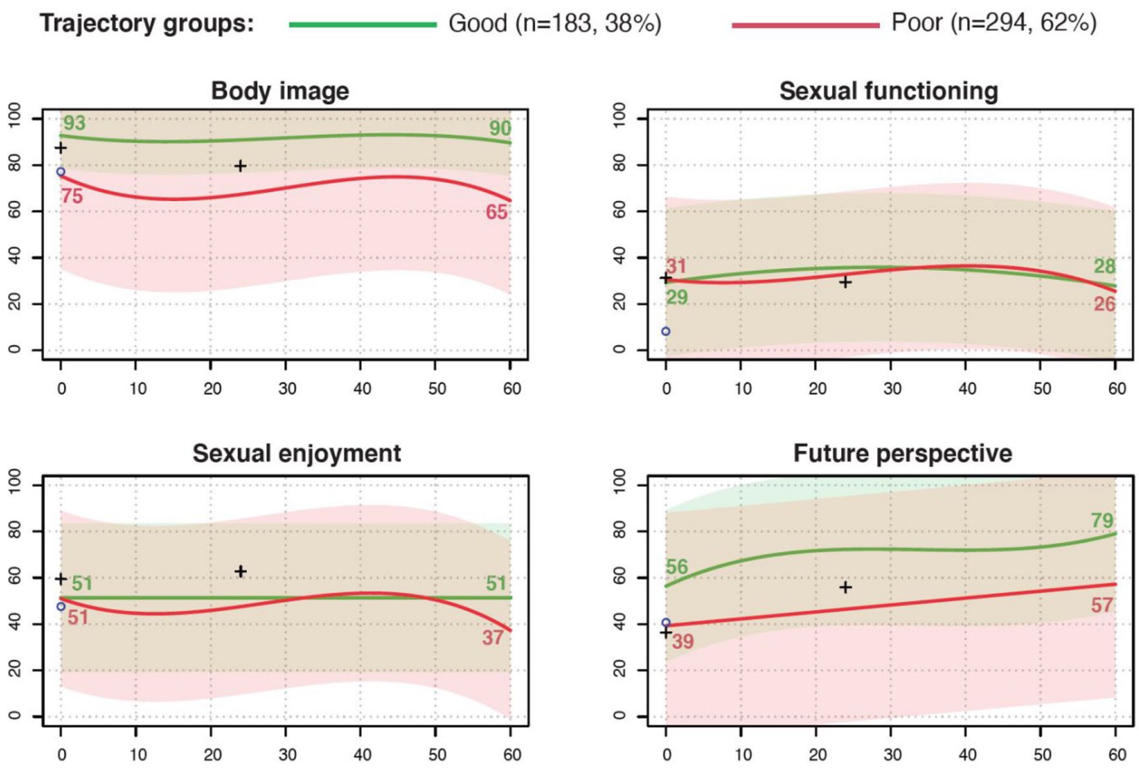

Figure 1. EORTC QLQ-BR23 functional scale scores across trajectory groups and months since breast cancer diagnosis.
The solid lines represent the predicted mean trajectories, with shaded regions indicating 95% pointwise prediction intervals. Higher scores represent greater functionality. Plus signs represent the scores for YWBCs in the CaMISS study,[39] while blue circles indicate values from the original QLQ-BR23 study for patients with a Karnofsky Performance Status ⩽70.[25]
EORTC QLQ-BR23, European Organization for the Research and Treatment of Cancer Breast Cancer module; YWBC, young women with breast cancer.

and symptom scales of the QLQ-BR23 questionnaire at the different time points.

Predictors of trajectory membership

According to the univariable logistic models, patients with public insurance (odds ratio (OR) 0.46, 95% confidence interval (CI) 0.19–1.00, $p = 0.061$), those with human epidermal growth factor receptor 2 (HER2)-positive BC (OR 0.61, 95% CI 0.38–0.98, $p = 0.039$), and those receiving chemotherapy without anthracycline regimens (OR 0.45, 95% CI 0.21–0.94, $p = 0.036$) were less likely to belong to the poor trajectory group (Table 2). These predictors were then included in a multivariable model (Table 3), and after adjusting for stage, two factors remained significantly associated with not belonging to the poor trajectory group: HER2-positive BC (OR 0.41, 95% CI 0.16–0.90, $p = 0.035$) and public health insurance (OR 0.57, 95% CI 0.35–0.94, $p = 0.028$).

We first sought to explore the differences between patients with public health insurance and those with private health insurance. We found that women with private insurance were more likely to be in a partnership (85% vs 63%, $p = 0.010$) and employed (56% vs 36%, $p = 0.020$), to have regularly consumed alcohol at baseline (41% vs 27%, $p = 0.090$), and to have triple-negative breast cancer (38% vs 25%, $p = 0.271$). Similarly, we sought to identify differences among women with and without HER2-positive BC and found that the former were more likely to be on non-anthracycline regimens (12% vs 6%, $p < 0.001$) and not on endocrine therapy (34% vs 7%, $p < 0.001$).

Discussion

In this study, we evaluated longitudinal changes over 5 years in the QoL of YWBC from the Joven & Fuerte cohort using a BC-specific questionnaire. Most patients ($n = 294$, 62%) were assigned to the poor trajectory group. Moreover, the

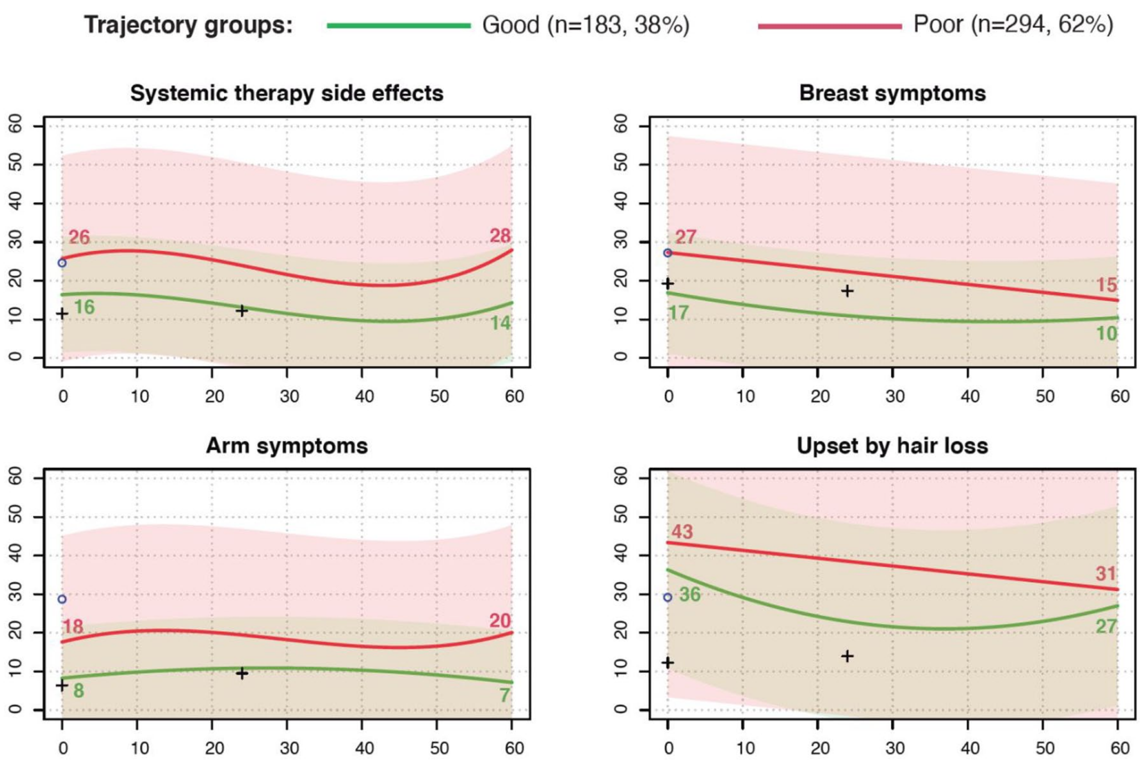

Figure 2. EORTC QLQ-BR23 symptom scale scores across trajectory groups and months since breast cancer diagnosis.

The solid lines represent the predicted mean trajectories, with shaded regions indicating 95% pointwise prediction intervals. Higher scores represent worse symptoms. Plus signs represent the scores for YWBC in the CaMISS study,[39] while blue circles indicate values from the original QLQ-BR23 study for patients with a Karnofsky Performance Status ⩽70.[25]

EORTC QLQ-BR23, European Organization for the Research and Treatment of Cancer Breast Cancer module; YWBC, young women with breast cancer.

questionnaire domains with the most significant impairment were those related to sexual functioning and enjoyment, future perspective, systemic therapy side effects, and being upset by hair loss.

Research on the QoL of patients with BC is quite valuable, as efforts to improve the QoL directly benefit patients in diverse areas of their lives.[32,33] To this end, advanced statistical methods, such as group-based multivariate trajectory modeling, offer valuable insights by identifying subgroups of patients at greater risk for significant QoL deterioration—which might be missed when assessing average changes across the population. Through this approach, we identified two distinct subgroups within our population of YWBC: those with a good QoL trajectory and those with a poor QoL trajectory over time.

QoL is one of the most essential endpoints for patients with metastatic cancer. Patients with metastatic disease seek to live as long as possible while maintaining good QoL and overall functionality.[34] In our cohort, 11% were diagnosed with de novo metastatic BC, which is higher than the 6%–8% reported in other registries for YWBC.[35] While these patients face unique mental and emotional challenges compared to those with a curable disease, their QoL varies based on individual life circumstances.[34] Given these complexities, we plan to explore how QoL evolves over time in patients with de novo metastatic BC in a future study.

Alarmingly, nearly two-thirds of our population were clustered into the poor trajectory group. This proportion is higher than that reported in other studies, in which the proportion in groups with a poor or deteriorating trajectory ranged from 6% to 59%.[15–20,36] One potential explanation for this discrepancy is that prior studies focused primarily on older populations. A meta-analysis of 9012 patients with BC revealed a significant association between age and improved

Table 2. Univariable binary logistic regression analysis of factors associated with trajectory group classification (vs reference "Good," $n = 183$; 38%).

Factor	Poor trajectory group $n = 294$ (62%)	
	OR (95% CI)	p
Age, ⩽35 vs >35	1.00 (0.69–1.45)	0.999
Education level, ⩽high school vs >high school	0.89 (0.61–1.29)	0.528
Marital status, partnered vs not	1.35 (0.91–1.99)	0.132
Number of children, ⩾1 vs no	1.06 (0.68–1.64)	0.801
Employed, yes vs no	1.37 (0.93–2.03)	0.117
Household income MXN $, ⩾6800 vs <6800	1.08 (0.72–1.63)	0.695
Type of insurance, public vs private	0.46 (0.19–1.00)	0.061
Regular exercise, yes vs no	0.85 (0.58–1.24)	0.395
Regular smoking, yes vs no	1.05 (0.67–1.66)	0.824
Regular alcohol consumption, yes vs no	1.21 (0.79–1.87)	0.379
Body mass index, underweight or normal vs overweight or obese	1.16 (0.80–1.70)	0.438
Stage, III vs 0–I–II	1.13 (0.78–1.66)	0.517
Subtype, HER2+ vs HR+HER2–	0.61 (0.38–0.98)	**0.039**
Subtype, TNBC vs HR+HER2–	0.85 (0.54–1.32)	0.459
Surgery, breast-conserving surgery vs mastectomy	0.89 (0.58–1.37)	0.595
Surgery, none vs mastectomy	0.30 (0.04–1.56)	0.169
Axillary surgery, sentinel node biopsy vs axillary dissection	1.06 (0.72–1.56)	0.766
Axillary surgery, none vs axillary dissection	0.48 (0.09–2.20)	0.338
No CT vs anthracycline-based CT	0.89 (0.50–1.62)	0.703
Non-containing anthracycline CT vs anthracycline-based CT	0.45 (0.21–0.94)	**0.036**
No CT vs neoadjuvant CT	1.03 (0.57–1.82)	0.915
Adjuvant CT vs neoadjuvant CT	1.23 (0.83–1.84)	0.311
No hormone therapy vs tamoxifen and/or aromatase inhibitor	1.18 (0.77–1.80)	0.442
Containing LHRHa vs tamoxifen and/or aromatase inhibitor	1.29 (0.79–2.11)	0.311
Radiotherapy, yes vs no	1.16 (0.77–1.75)	0.476

CI, confidence interval; CT, chemotherapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LHRHa, luteinizing hormone releasing hormone analog; MXN $, Mexican peso; OR, odds ratio; TNBC, triple-negative breast cancer.

QoL.[33] In addition, our greater proportion of patients with poor trajectories may be due to our use of a BC-specific QoL questionnaire and our decision to include all QoL domains in the analysis rather than to focus on a single domain. Previous research has shown that the number of trajectory groups identified can vary depending on the specific QoL domain studied.[17,36]

Table 3. Multivariable binary logistic regression of factors associated with trajectory group classification (vs reference "Good," *n* = 183; 38%).

Factor	Poor trajectory group *n* = 294 (62%)	
	aOR (95% CI)	*p*
Type of insurance, public vs private	0.41 (0.16–0.90)	0.035
Stage, III vs 0–I–II	1.19 (0.78–1.83)	0.411
Subtype, HER2+ vs HR+HER2–	0.57 (0.35–0.94)	0.028
Subtype, TNBC vs HR+HER2–	0.71 (0.44–1.16)	0.169
No CT vs anthracycline-based CT	0.73 (0.37–1.42)	0.342
Non-containing anthracycline CT vs anthracycline-based CT	0.47 (0.21–1.06)	0.069

aOR, adjusted odds ratio; CI, confidence interval; CT, chemotherapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; TNBC, triple-negative breast cancer.

Improving patient care starts by identifying patients with poor QoL and understanding their needs. To achieve this, it is essential to integrate the regular and systematic use of patient-reported outcome measures when treating YWBC, as these tools can identify patients who require additional support.[37] Our study provides specific QoL scores that can guide clinicians to identify these patients throughout follow-up. In addition, implementing navigation programs that use these scores can facilitate timely referrals to services such as psychological support, external prostheses, and sexual health counseling.[38]

Assessing patients' QoL during active treatments such as chemotherapy and breast surgery is crucial, but ongoing monitoring beyond treatment completion is equally important. Our findings highlight that a significant impact on the QoL of patients occurs during treatment with active therapies, and the effect can persist for up to 5 years after diagnosis, underscoring the need for long-term follow-up and comprehensive care.

Since the QLQ-BR23 questionnaire lacks defined thresholds for clinically significant impairments, we compared our mean scores to those reported for YWBC in the CaMISS study, a multicenter prospective cohort that evaluated changes in the QoL of patients with BC in Spain.[39] Both trajectory groups in our study had worse scores in sexual enjoyment, systemic therapy side effects, arm symptoms, and distress from hair loss, both at baseline and at the 2-year follow-up, than did YWBC in the CaMISS study. Furthermore, the poor trajectory group in our study had worse scores across all other QoL domains than did the CaMISS cohort. However, that study did not provide detailed data on young patients, limiting direct comparisons.

When comparing our scores to the baseline scores of patients from the original QLQ-BR23 study with a Karnofsky Performance Status $\leqslant 70$,[25] we found that our poor trajectory group had similar baseline scores, except for better scores in sexual functioning and arm symptoms. Notably, both trajectory groups in our study reported greater distress from hair loss than those with a Karnofsky Performance Status $\leqslant 70$, highlighting the significant emotional impact of hair loss in young patients.

Unsurprisingly, QoL scores related to sexual health declined in our population; as YWBC often experience sexual health issues due to both cancer itself and its treatments.[40] Mastectomy can impact desire, arousal, and achieving orgasm,[41] while chemotherapy and endocrine therapies frequently cause decreased libido, vaginal dryness, and dyspareunia.[8,41,42] In our study, most women received these therapies, which likely explains the decline in scores during the first year and persistent systemic therapy side effects at year 5. Our previous research using specific sexual questionnaires also found high rates of sexual dysfunction and low satisfaction at year 5.[43,44] These findings emphasize the need for better sexual health support and effective interventions for YWBC.

Fear of recurrence is one of the most commonly reported concerns among cancer survivors, particularly for younger individuals who are at a high risk of recurrence.[45,46] In our study, both trajectory groups showed improvement in the future perspective domain scores over time, which is consistent with previous research on YWBC, in which patients and their families became less concerned about recurrence over time.[47] Notably, by the end of the study, patients in the poor trajectory group had reached the baseline levels of those in the good trajectory group. These findings suggest that patients in the poor trajectory group might benefit from psychoeducational interventions aimed at enhancing coping skills and alleviating their fear of recurrence.

Distress from hair loss was initially high in both groups but improved over time. Chemotherapy-induced alopecia is the most visible and emotionally challenging side effect of common chemotherapy agents and has a profound impact on patients' emotional and social well-being.[7,48] In our cohort, most women received chemotherapy regimens containing anthracyclines and taxanes, known to induce hair follicle apoptosis,[48] likely contributing to early distress. Fortunately, management strategies such as wearing wigs and wraps and the use of scalp-cooling devices can help lessen this side effect and therefore should be discussed with the patient before starting treatment.[7] Scalp cooling is more effective when taxanes precede anthracyclines rather than vice versa.[49] Persistent distress may stem from hair thinning caused by endocrine therapy. Interventions such as topical minoxidil, 5-alpha reductase inhibitors, and supplementation with vitamin C and omega-3 fatty acids may improve hair loss and should be considered by clinicians.[50]

In this study, patients with public health insurance (87%) were more likely to belong to the good trajectory group. In Mexico, 92% of the population has public insurance,[51] but many pay out-of-pocket for private services, which offer better quality care, medication availability, and shorter wait times.[52] Conversely, private insurance holders can also access public healthcare.[51,52] Thus, other factors may explain the impact of insurance type on QoL. In our cohort, women with private insurance were more likely to be in a relationship and to have habitually consumed alcohol at baseline than those with public insurance. We previously reported that these factors could contribute to a poorer QoL.[10,43,53] In addition, patients with private insurance often come from higher socioeconomic backgrounds and may not face the same daily struggles as those with lower socioeconomic status. Consequently, cancer tends to become their primary concern, whereas for patients from lower socioeconomic backgrounds, cancer is one of the many challenges they face. This may explain the better QoL observed in the latter group.

Patients with HER2-positive BC had better QoL than those without overexpression of this biomarker. In our cohort, 22% of patients had HER2-positive tumors, a proportion consistent with previous reports for young patients.[5] Targeted therapies for HER2-positive BC generally have a favorable risk–benefit profile, with common side effects being fever, chills, and other self-limiting symptoms.[54] In addition, our findings suggest that these patients were less likely to receive anthracycline-based regimens and underwent less endocrine therapy, which may contribute to their better QoL. Previous studies have shown that patients receiving trastuzumab experience greater QoL improvements than those without.[55,56] One hypothesis is that reducing tumor burden enhances physical well-being and positively impacts QoL in this patient group.[57]

This study has some limitations that should be considered when interpreting the results. First, our findings are based on patient-reported outcomes, which are susceptible to reporting bias. While the data were collected prospectively, there was missing information, especially at later time points, which may have affected our estimates, as shown in the Supplemental Figure 1. Moreover, 12% of our patients completed the questionnaire only once, which could have altered the estimates for the overall population. In addition, unmeasured confounding factors, such as relationship dynamics, the use of medications that could affect sexual health, or participation in postoperative rehabilitation programs, may have influenced our results.

Conclusion

This study offers a comprehensive overview of the longitudinal changes in QoL among YWBC in Mexico, highlighting critical areas of QoL impairment. The notably high proportion of patients experiencing poor QoL demands special attention and should be carefully considered by the entire medical team when treating young women. Future research should prioritize developing interventions that address the unique needs of these patients and enhance the multidimensional aspects of their QoL.

Declarations

Ethics approval and consent to participate

The study protocol received approval from the Research Ethics Committees at the Instituto Nacional de Cancerología (#OM CM-J 03) and the School of Medicine at Instituto Tecnológico y de Estudios Superiores de Monterrey. Consent to participate: All patients consented to participate in this study.

Consent for publication

Not applicable.

Author contributions

Bryan F. Vaca-Cartagena: Conceptualization; Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

Fernanda Mesa-Chavez: Data curation; Investigation; Writing – review & editing.

Ana S. Ferrigno Guajardo: Conceptualization; Data curation; Investigation; Writing – review & editing.

Hatem A. Azim Jr: Conceptualization; Investigation; Supervision; Writing – review & editing.

Federico Rotolo: Formal analysis; Investigation; Writing – review & editing.

Alejandra Platas: Investigation; Writing – review & editing.

Alan Fonseca: Data curation; Investigation; Writing – review & editing.

Marlid Cruz-Ramos: Conceptualization; Investigation; Writing – review & editing.

Ana Rodriguez: Investigation; Writing – review & editing.

Alejandro Mohar: Conceptualization; Investigation; Writing – review & editing.

Cynthia Villarreal-Garza: Conceptualization; Investigation; Methodology; Resources; Supervision; Writing – review & editing.

Acknowledgements

We thank all the patients who participated in the Joven & Fuerte cohort. Without their selfless participation, this study would not have been possible. We also extend our sincere gratitude to all the collaborators who have been dedicated to this study since its beginning. We thank Springer Nature Services for helping with the scientific editing of the manuscript.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

H.A.A. Jr: Consulting: Evexta Bio, Pep Therapy, Linkinvax. F.R.: Financial: Sanofi. Stock and other ownership interests: Innate Pharma. C.V.-G.: Grants: Pfizer, AstraZeneca, and Gilead. Honoraria: MSD, AstraZeneca, Eli Lilly, and Novartis. Support for attending meetings and travel: Novartis, MSD, and AstraZeneca. No other disclosures were reported.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, C.V.-G., upon reasonable request at the following email address: cynthia.villarreal@tecsalud.mx. Investigators are invited to submit study proposal requests detailing research questions and hypotheses to receive access to these data.

ORCID iDs

Bryan F. Vaca-Cartagena https://orcid.org/0000-0003-3970-3259

Fernanda Mesa-Chavez https://orcid.org/0000-0003-4723-1837

Ana S. Ferrigno Guajardo https://orcid.org/0000-0003-1855-1196

Cynthia Villarreal-Garza https://orcid.org/0000-0003-3587-339X

Supplemental material

Supplemental material for this article is available online.

References

1. Siegel RL, Giaquinto AN and Jemal A. Cancer statistics, 2024. *CA Cancer J Clin* 2024; 74: 12–49.

2. Giaquinto AN, Sung H, Newman LA, et al. Breast cancer statistics 2024. *CA Cancer J Clin* 2024; 74: 477–495.

3. Villarreal-Garza C, Aguila C, Magallanes-Hoyos MC, et al. Breast cancer in young women in

Latin America: an unmet, growing burden. *Oncologist* 2013; 18: 1298–1306.

4. Cazap E. Breast cancer in Latin America: a map of the disease in the region. *Am Soc Clin Oncol Educ Book* 2018; 38: 451–456.
5. Azim HA and Partridge AH. Biology of breast cancer in young women. *Breast Cancer Res* 2014; 16: 427.
6. Partridge AH, Hughes ME, Ottesen RA, et al. The effect of age on delay in diagnosis and stage of breast cancer. *Oncologist* 2012; 17: 775–782.
7. Kuderer NM, Desai A, Lustberg MB, et al. Mitigating acute chemotherapy-associated adverse events in patients with cancer. *Nat Rev Clin Oncol* 2022; 19: 681–697.
8. Lustberg MB, Kuderer NM, Desai A, et al. Mitigating long-term and delayed adverse events associated with cancer treatment: implications for survivorship. *Nat Rev Clin Oncol* 2023; 20: 527–542.
9. Howard-Anderson J, Ganz PA, Bower JE, et al. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. *J Natl Cancer Inst* 2012; 104: 386–405.
10. Vaca-Cartagena BF, Ferrigno Guajardo AS, Azim HA Jr, et al. Describing quality of life trajectories in young Hispanic women with breast cancer: 5-year results from a large prospective cohort. *Breast* 2025; 79: 103866.
11. Champion VL, Wagner LI, Monahan PO, et al. Comparison of younger and older breast cancer survivors and age-matched controls on specific and overall quality of life domains. *Cancer* 2014; 120: 2237–2246.
12. Ganz PA, Greendale GA, Petersen L, et al. Breast cancer in younger women: reproductive and late health effects of treatment. *J Clin Oncol* 2003; 21: 4184–4193.
13. Villarreal-Garza C, Vaca-Cartagena BF, Becerril-Gaitan A, et al. Abstract P4-10-20: quality of life in Mexican young women with locally-advanced breast cancer: a cohort study. *Cancer Res* 2022; 82: P4-10-20.
14. Roine E, Sintonen H, Kellokumpu-Lehtinen P-L, et al. Long-term health-related quality of life of breast cancer survivors remains impaired compared to the age-matched general population especially in young women. Results from the prospective controlled BREX exercise study. *Breast* 2021; 59: 110–116.
15. Di Meglio A, Havas J, Gbenou AS, et al. Dynamics of long-term patient-reported quality of life and health behaviors after adjuvant breast cancer chemotherapy. *J Clin Oncol* 2022; 40: 3190–3204.
16. Park J-H, Jung YS, Kim JY, et al. Trajectories of health-related quality of life in breast cancer patients. *Support Care Cancer* 2020; 28: 3381–3389.
17. Goyal NG, Levine BJ, Van Zee KJ, et al. Trajectories of quality of life following breast cancer diagnosis. *Breast Cancer Res Treat* 2018; 169: 163–173.
18. Franzoi MA, Di Meglio A, Michiels S, et al. Patient-reported quality of life 6 years after breast cancer. *JAMA Netw Open* 2024; 7: e240688.
19. Durá-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). *Psychooncology* 2017; 26: 1914–1921.
20. Park J-H, Jung YS, Kim JY, et al. Trajectories of quality of life in breast cancer survivors during the first year after treatment: a longitudinal study. *BMC Womens Health* 2023; 23: 12.
21. Villarreal-Garza C, Platas A, Miaja M, et al. Young women with breast cancer in Mexico: results of the pilot phase of the Joven & Fuerte prospective cohort. *JCO Glob Oncol* 2020; 6: 395–406.
22. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform* 2019; 95: 103208.
23. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42: 377–381.
24. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; 61: 344–349.
25. 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: 2756–2768.
26. Fayers P, Aaronson NK, Bjordal K, et al. *EORTC QLQ-BR23 scoring manual*. Brussels: European Organisation for Research and Treatment of Cancer, 2001.

27. Rodriguez-Gonzalez A, Velasco-Durantez V, Martin-Abreu C, et al. Fatigue, emotional distress, and illness uncertainty in patients with metastatic cancer: results from the prospective NEOETIC_SEOM study. *Curr Oncol* 2022; 29: 9722–9732.

28. Nagin DS. *Group-based modeling of development*. Cambridge: Harvard University Press, 2005.

29. Nagin DS, Jones BL, Passos VL, et al. Group-based multi-trajectory modeling. *Stat Methods Med Res* 2018; 27: 2015–2023.

30. Magrini A. Assessment of agricultural sustainability in European Union countries: a group-based multivariate trajectory approach. *Adv Stat Anal* 2022; 106: 673–703.

31. R Core Team. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, https://www.r-project.org/ (2022, accessed 8 May 2024).

32. Heidary Z, Ghaemi M, Hossein Rashidi B, et al. Quality of life in breast cancer patients: a systematic review of the qualitative studies. *Cancer Control* 2023; 30: 1–10.

33. Javan Biparva A, Raoofi S, Rafiei S, et al. Global quality of life in breast cancer: systematic review and meta-analysis. *BMJ Support Palliat Care* 2023; 13: e528–e536.

34. Mertz S, Benjamin C, Girvalaki C, et al. Progression-free survival and quality of life in metastatic breast cancer: the patient perspective. *Breast* 2022; 65: 84–90.

35. Xiao Q, Zhang W, Jing J, et al. Patterns of de novo metastasis and survival outcomes by age in breast cancer patients: a SEER population-based study. *Front Endocrinol (Lausanne)* 2023; 14: 1184895.

36. Sella T, Yue Z, Ruddy K, et al. Abstract PO2-12-01: five-year quality of life (QOL) trajectories among young breast cancer (BC) survivors. *Cancer Res* 2024; 84: PO2-12-01.

37. Tevis SE, James TA, Kuerer HM, et al. Patient-reported outcomes for breast cancer. *Ann Surg Oncol* 2018; 25: 2839–2845.

38. Mesa-Chavez F, Labra L, Rodriguez A, et al. Abstract PO4-12-01: navigation program for timely needs assessment and referral to appropriate services among young breast cancer patients in Mexico. *Cancer Res* 2024; 84: PO4-12-01.

39. Miret C, Orive M, Sala M, et al. Reference values of EORTC QLQ-C30, EORTC QLQ-BR23, and EQ-5D-5L for women with non-metastatic breast cancer at diagnosis and 2 years after. *Qual Life Res* 2023; 32: 989–1003.

40. Bober SL and Varela VS. Sexuality in adult cancer survivors: challenges and intervention. *J Clin Oncol* 2012; 30: 3712–3719.

41. Boswell EN and Dizon DS. Breast cancer and sexual function. *Transl Androl Urol* 2015; 4: 160.

42. Cucciniello L, Garufi G, Di Rienzo R, et al. Estrogen deprivation effects of endocrine therapy in breast cancer patients: incidence, management and outcome. *Cancer Treat Rev* 2023; 120: 102624.

43. Ferrigno Guajardo A, Fonseca A, Miaja M, et al. Factors associated with sexual function and sexual satisfaction in young women with breast cancer. *J Clin Oncol* 2024; 42: 12062–12062.

44. Ferrigno Guajardo A, Vaca-Cartagena BF, Mesa-Chavez F, et al. Sexual function and satisfaction in young women with breast cancer: a 5-year prospective study. *JNCI Cancer Spectr* 2024; 8(6): pkae111.

45. Azim HA, Michiels S, Bedard PL, et al. Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling. *Clin Cancer Res* 2012; 18: 1341–1351.

46. Villarreal-Garza C, Becerril Gaitan A, Vaca-Cartagena B, et al. High-early recurrence rate in a cohort of young women with breast cancer in Mexico. *J Clin Oncol* 2021; 39: e12560.

47. Schapira L, Zheng Y, Gelber SI, et al. Trajectories of fear of cancer recurrence in young breast cancer survivors. *Cancer* 2022; 128: 335–343.

48. Dunnill CJ, Al-Tameemi W, Collett A, et al. A clinical and biological guide for understanding chemotherapy-induced alopecia and its prevention. *Oncologist* 2018; 23: 84–96.

49. Villarreal-Garza C, Mesa-Chavez F, Garza-Ledezma MRA, et al. Impact of chemotherapy regimen and sequence on the effectiveness of scalp cooling for alopecia prevention. *Breast Cancer Res Treat* 2021; 185: 453–458.

50. Karatas F, Sahin S, Sever AR, et al. Management of hair loss associated with endocrine therapy in patients with breast cancer: an overview. *Springerplus* 2016; 5: 585.

51. Urquieta-Salomón JE and Villarreal HJ. Evolution of health coverage in Mexico: evidence of progress and challenges in the Mexican health system. *Health Policy Plan* 2016; 31: 28–36.

52. González Block MÁ, Reyes Morales H, Hurtado LC, et al. Mexico health system review. *Health Syst Transit* 2020; 22: 1–222.

53. Vaca-Cartagena BF, Guajardo ASF, Azim HA, et al. 303P Predicting quality of life trajectories in young women with breast cancer: 5-year results from a large prospective cohort. *Ann Oncol* 2024; 35: S341–S342.

54. Moja L, Tagliabue L, Balduzzi S, et al. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev* 2012; 2012: CD006243.

55. Khoirunnisa SM, Suryanegara FDA, Setiawan D, et al. Health-related quality of life in Her2-positive early breast cancer woman using trastuzumab: a systematic review and meta-analysis. *Front Pharmacol* 2023; 14: 1–14.

56. Syrios J, Pappa E, Volakakis N, et al. Real-world data on health-related quality of life assessment in patients with breast cancer receiving subcutaneous trastuzumab. *Breast Cancer (Auckl)* 2018; 12: 1–10.

57. Osoba D, Slamon DJ, Burchmore M, et al. Effects on quality of life of combined trastuzumab and chemotherapy in women with metastatic breast cancer. *J Clin Oncol* 2002; 20: 3106–3113.