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Health-Related Quality of Life in Patients with Breast Cancer in Latin America and the Caribbean: A Systematic Review and Meta-Analysis

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Disclosures of potential conflicts of interest may be found at the end of this article.

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ABSTRACT

Background and Objectives. Breast cancer (BC) is the most common cancer in women. It imposes a huge disease burden and a significant impact on health-related quality of life (HRQoL). Our study focused on HRQoL of patients with BC in Latin America and the Caribbean (LAC). We conducted a systematic review to identify relevant articles published between 2008 and August 2018. We conducted several meta-analyses and subgroup analyses by country, disease stage, and instrument used (Prospective Register Of Systematic Reviews registration number: CRD42018106835).

Results. From 2,265 initial references, we finally included 75 articles (8,806 participants) that assessed HRQoL. The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 and B23 modules (34 studies; 8 countries; 4,866 participants) were the most used instruments, followed by the Short Form 36-item, the abbreviated version of the World Health Organization Quality of Life instrument, and the Functional Assessment of Cancer Therapy – Breast instrument. Only four studies reported specific HRQoL data of patients with metastatic disease. Half the studies were rated as having moderate quality (38/75), and 38% (29/75) as high quality. We identified substantial heterogeneity. As expected, the meta-analyses revealed that patients with metastatic disease reported lower HRQoL values and high symptom burden compared with patients at earlier stages. Similar results can be observed when we compared patients with early breast cancer in active treatment phases versus those in follow-up.

Conclusion. This study provides a synthesis of breast cancer HRQoL reported in LAC and exposes existing evidence gaps. Patients with BC in active treatment or with metastatic disease had worse HRQoL compared with survivors during the follow-up period. ***The Oncologist*** 2021;26:e794–e806

Implications for Practice: This systematic review provides an exhaustive synthesis of breast cancer health-related quality of life in women in the Latin American and Caribbean region. Patients with breast cancer in active treatment or with metastatic disease had worse health-related quality of life compared with survivors during the different follow-up periods. This study also shows important evidence and methods gaps that can help inform future research.

INTRODUCTION

Breast cancer (BC) is the most frequent tumor and the leading cause of death among women worldwide [1]. Developing countries are more affected by BC, representing roughly half of the incidence and 60% of deaths. BC is the most frequent cancer and cause of specific death among women living in Latin America and the Caribbean (LAC) region, with 200,000 new cases and more than 52,000 deaths per year [1].

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The diagnosis of BC causes a great physical, psychological, and economic impact on the patients and their families and on their surrounding social networks. It entails a modification of the natural course of personal life and family dynamics. The news of the diagnosis imposes a significant impact on health-related quality of life (HRQoL). The actual symptoms, the potential changes perceived regarding life expectancy, and the menace of potential adverse events from treatment significantly affect its different domains.

Quality of life is a subjective, multidimensional, and dynamic concept that includes physical, emotional, social, and functional well-being. According to the World Health Organization, it refers to the person's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns [2]. But defining HRQoL is more challenging, and multiple definitions can be found in the literature [3]. HRQoL is a health-focused QoL concept that embraces aspects of health—both physical and mental—that influence QoL (e.g., "those aspects of self-perceived wellbeing that are related to or affected by the presence of disease or treatment" [3, 4]).

Many generic and disease-specific instruments have been developed and validated to measure HRQoL. Reference values for each instrument are necessary for assessing individual patients' data and comparing them with general or specific populations. Several studies have been performed to assess HRQoL in patients with BC and survivors living in LAC, but there is no study that has synthesized this body of evidence. Disparities in access to diagnosis as well as treatment of BC, and different sociocultural contexts across LAC countries, make it difficult to extrapolate reference values from other regions of the world or the use of normative data obtained in individual countries.

Our objective was to characterize the HRQoL in patients with BC living in LAC and to explore relationships with disease stage and treatment in real-world settings. We additionally aimed to provide a detailed analysis of the specific instruments used and their results. In order to accomplish this, we conducted a systematic review and meta-analysis. This study is part of a larger project that also intended to depict the costs of medical care, the loss of labor productivity of patients with BC, and the out-of-pocket expenditures of patients and their families in LAC. This study is being published separately.

MATERIALS AND METHODS

We followed the Meta-Analysis of Observational Studies in Epidemiology guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for reporting systematic reviews and meta-analyses [5, 6]. The protocol was registered on the International Centre for Reviews and Dissemination Prospective Register Of Systematic Reviews under the registration number CRD42018106835.

We performed a systematic search of published and unpublished data on the main international and regional databases: PubMed, LILACS, EMBASE, the CEA registry, CRD, EconLit, and PsycINFO. We also searched conference proceedings of international oncology societies' meetings. No language restriction was applied. The search strategy used is presented in supplemental online Table 1. The systematic search was performed on August 28, 2018.

Studies were included only if they reported results on HRQoL through a validated generic or specific HRQoL questionnaire in a sample of at least 20 patients (conventional cutoff) living in any LAC country. Exclusion criteria were the use of nonvalidated instruments to measure HRQoL, or a publication date prior to 2008. The integrated yield of searches was fed into the Covidence Systematic Review Software (Veritas Health Innovation, Melbourne, Australia) for independent screening by pairs of reviewers, out of a total of eight, and those studies potentially eligible were then selected for full text appraisal. For every study that met inclusion criteria, new pairs of reviewers independently extracted all relevant information and assessed their inherent risk of bias in a prepiloted Microsoft Excel (Microsoft Corporation, Redmond, WA) online spreadsheet for data extraction. Discrepancies were resolved by consensus of the whole team. To assess the risk of bias of the studies reporting HRQoL, we implemented the Mols et al. [7] quality assessment tool with modifications agreed upon by our team (supplemental online Table 2). Extracted data were synthesized using both descriptive and meta-analytic approaches by outcome measures.

HRQoL domains and scores were summarized using means, standard deviations, and 95% confidence intervals (95% CIs). Whenever missing, the 95% CIs for the mean were computed with the following formula: 95%CI = Media +/− [$Z\alpha/2$*(SD/$\sqrt{}$sample)] [8].

When the median and interquartile range were reported, we derived the mean and SD based on the methodology of Hozo et al. [9]. In those studies not reporting SD, we proceeded as follows: we initially considered the data from each of the studies of the same clinical group reporting a mean and SD in each score or domain. Then, for each study, the relative value of the SD was estimated in relation to the mean (relative SD study of i [RSDi]) = Mean i / SDi). The weighted average of this coefficient was then used to estimate the SD of the study or the studies that did not report it (imputed SD of study x = Mean x* weighted average of RSDs) [8]. When pooling data from different instruments, we initially mapped conceptually equivalent domains among instruments. Then, in order to be able to pool these results in the analysis, we proceeded to transform all individual domain scores to a common 0–100 scale.

Regarding statistical analyses, we first pooled the results from all individual studies using the random-effects model of meta-analysis described by DerSimonian and Laird [10]. Heterogeneity for each outcome among studies was assessed using the I-squared statistics. Results were considered heterogeneous if the I-squared statistic was >30% (30%–60%: moderate heterogeneity; >60%: substantial heterogeneity). Then we conducted the following subgroup analyses, prespecified in the study protocol, in order to assess heterogeneity of results: by questionnaire used, by stage of disease and being on treatment, and by country of origin of patients. To characterize the HRQoL of patients with BC throughout the various stages of the disease and treatment, three groups were defined: (a) those with early breast cancer (stage I, II, or III) who were receiving active treatment; (b) those with early breast cancer who had finished the treatment phase; and (c) patients with metastatic breast cancer (stage IV). Within the active treatment group, we included those studies that reported HRQoL of women who had undergone recent surgery (less than 6 months after surgery) or were receiving adjuvant treatment with chemotherapy or radiotherapy. Those studies with patients under hormonal treatment, or simply on follow-up, were included in the other group. If studies included more than 75% of participants in any of the subgroups considered, and no information was reported by the authors regarding subgroup-specific HRQoL, we assigned the results to the corresponding subgroup. Studies were excluded from the subgroup analysis when it was not possible to attribute the patients precisely to any of the prespecified subgroups owing to lack of information.

RESULTS

A total of 2,233 articles were retrieved from the initial search in different databases, and another 32 were found in the gray literature. After removal of 32 duplicate records, we screened 2,233 based on title and abstract. Of these, 1,848 were excluded because it was evident from the title or abstract that they were not relevant to the review. Three hundred eighty-five articles remained and were assessed for eligibility based on the full text. Finally, 267 studies were discarded because they did not meet inclusion criteria (93 wrong outcomes; 32 duplicated; 21 wrong study design; 18 no breast cancer–specific data; 15 wrong setting; 8 no country-specific data; 2 wrong patient population; and finally 78 because of other reasons like non-LAC country or publication date prior to 2008). Considering published and unpublished studies after screening and selection using the predefined inclusion and exclusion criteria, we finally included 75 studies encompassing 8,806 patients that assessed HRQoL. No additional studies were found from references cited in the papers included. The study flowchart is shown in Figure 1. The studies included and their characteristics are summarized in Table 1.

The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30 and B23 modules were the most used instruments. Most of the studies were from Brazil. Their sample size varied between 20 and 544 subjects. We found important heterogeneity in the age of participants, their means ranging from 42 to 62.7 years. The distribution of patients by countries and instrument to measure HRQoL is shown in Table 2.

Most of the studies included patients in early (stage I–II) and locally advanced (III) stages (36 studies; *n* = 4,288 patients). Some studies included all stages of the disease, but more than 75% were in stage I, II, or III (10 studies, *n* = 1,235). Regarding metastatic disease, 5.7% of studies (18 studies; *n* = 505) included patients in this stage, but only in 4 studies (four countries; *n* = 315) were results reported for this specific group. Two of them included only patients in this stage (*n* = 147).

We found no studies reporting HRQoL individual data according to any of the common BC molecular subtypes (i.e., luminal A; luminal B; triple-negative/basal-like or human epidermal growth receptor 2 [HER2]-enriched). Of the 75 studies included, 50% were published before 2014 (38 studies; *n* = 4,275). The I2 statistic in the meta-analyses of HRQoL was higher than 75% in all countries and virtually with all instruments, and particularly high with the EORTC C30 and B23 (information available on demand), denoting substantial heterogeneity.

Risk of Bias Assessment

Half of the studies were rated as having moderate quality (38/75), and 38% (29/75) were considered high quality. The mean quality score was 7.36. However, most studies had a high risk of selection bias. Also, most studies (65%; 49/75) did not describe the overall response rates (or when stated, they were lower than 75%) or the way in which sample patients were drawn (77%; 58/75). In those that did, methodological shortcomings consisted mainly of the lack of information on characteristics of nonresponders. Many studies included did report on all questionnaire domains (23%, 17/75) or even on position or dispersion of statistical parameters (20%; 15/75).

Pooled Estimates of HRQoL

In Tables 3 and 4, we show the results of the meta-analyses by HRQoL instruments and disease stage. Through random-effects models, we estimated that patients with stage IV disease had worse HRQoL than earlier stages. As expected, we found very high levels of heterogeneity among instruments, and domains, even when stratifying by relevant subgroups. Thus, we consider that the confidence intervals of the pooled estimates are more meaningful than the central estimate.

HRQoL with EORTC QLQ C30 and B23 Subscale Questionnaires

A total of 34 articles (eight countries; *n* = 4,866) reported HRQoL with EORTC QLQ-C30. Total sample sizes ranged from 22 to 544 patients, and the average age of participants from 42 to 62.7 years. Fifty-three percent of studies were rated as moderate quality (18/34), and 32% (11/34) as high quality. The mean quality score was 6.52. The pooled scores for global health status, symptom, and functional scales, broken down by stage of the disease and treatment, are shown in Table 3.

Mean scores of global health status and functional scales domains (except for the social functioning score) of patients with stage IV disease were lower than those of patients with stage I, II, or III, regardless of the treatment phase. Similar results were observed for all symptom scales.

In general, comparisons between patients with early BC show that mean scores are higher in most scales in the follow-up group versus those in active treatment. More pronounced differences were observed in the global health status, physical, role, and social functioning domains.

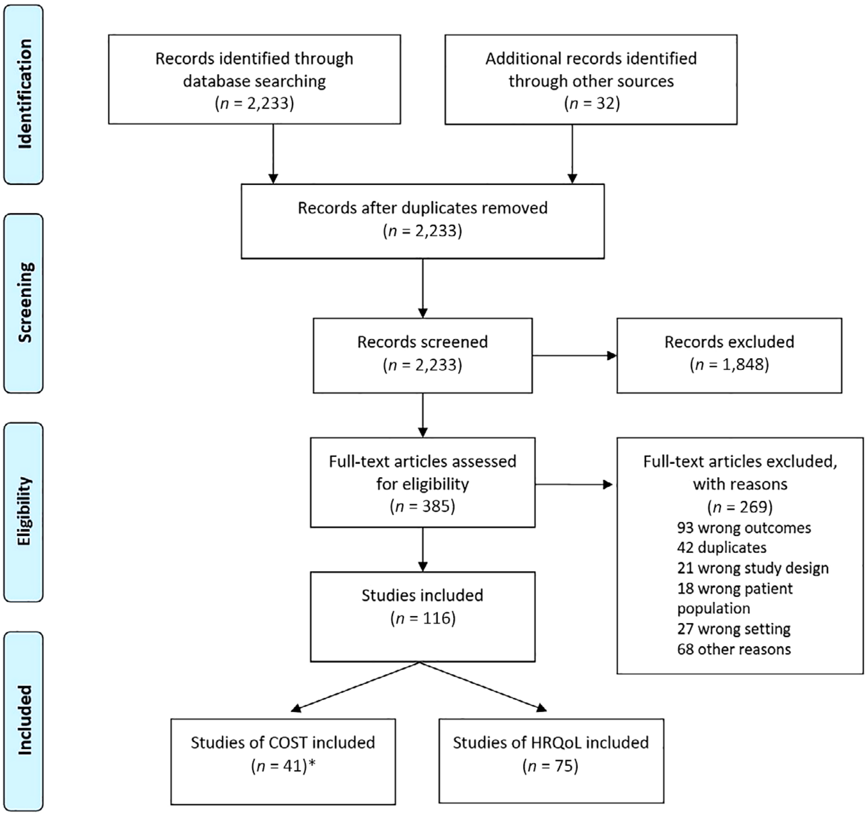

Figure 1. Study flowchart.
Abbreviation: COST, costs of medical care; HRQoL, health-related quality of life.

Twenty-five articles (seven countries; *n* = 4,342) reported HRQoL with the EORTC QLQ-B23 module (Table 3). Patients with metastatic disease reported lower HRQoL and high symptom burden compared with patients with earlier stages. Similar results can be observed when comparing patients with active treatment versus those in follow-up.

HRQoL with the SF-36 Health Survey

A total of 19 articles (six countries; *n* = 1,675) reported HRQoL with the Short Form 36-item (SF-36) in patients with BC living in LAC. Total sample sizes of the studies ranged from 22 to 221 patients, and the average age of participants ranged from 48.1 to 57.2 years. Fifty-two percent of studies were rated as moderate quality (10/19), and 48% (9/19) attained scores above 75% of the maximum score. The maximum attainable score ranged from 5 to 10 points with a mean quality score of 7.42.

Seventeen studies (six countries; *n* = 1,475) that measured HRQoL in early (I and II) and locally advanced (III) stages, and only one study from Colombia (*n* = 4) that disaggregated data of patients with metastatic disease, were included in subgroup meta-analysis. Given these assumptions, the pooled mean reported in Table 4 is assumed as representative of the population in stages I, II, and III, whereas the HRQoL of metastatic disease IV is only represented by four patients. Comparison of limited versus metastatic disease groups shows significantly worse HRQoL scores in patients with advanced BC. However, the small number of patients included in this last group limits the significance of the observed difference. A very similar mean score was observed between patients in early breast cancer, with the exception of bodily pain and vitality domains.

HRQoL with the FACT-B Instrument

Of the 75 studies included in the systematic review, HRQoL was assessed by the Functional Assessment of Cancer Therapy – Breast (FACT-B) instrument in 11 studies (four countries; *n* = 1,057). Most studies were performed in Brazil (*n* = 6). Sample sizes of the studies ranged from 20 to 198 patients, and the average age of participants ranged from 40 to 60.7 years. Sixty-two percent of the studies (6/11) attained scores above 75% of the maximum score, whereas the rest were rated as moderate quality. The maximum attainable score ranged from 5 to 9 points with a mean quality score of 7.36 (Table 4).

In the meta-analysis of the FACT-B questionnaire, we found significant impairment in the HRQoL of patients with stage IV disease. Meaningful lower values in physical and emotional domains' estimates were observed in patients in the subsequent cross-sectional surveys through the natural disease evolution of these patients.

Table 1. Characteristics of the included health-related quality of life studies by instrument

Author	Year	Country	Instrument	Participants	Mean age (yr)	Cancer stage included	Patients in active treatment	Quality assessment
Gercovich [11]	2012	Argentina	EORTC QLQ-C30	72	56.0	All[a]	Yes	Low
Nicolussi [12]	2011	Brazil	EORTC QLQ-C30	35	52.7	All	Yes	Moderate
Garabeli [13]	2012	Brazil	EORTC QLQ-C30	202	53.8	I–II and III	No	Moderate
Moros [14]	2010	Chile	EORTC QLQ-C30	22	49.0	I–II and III	Yes	High
Finck [15]	2018	Colombia	EORTC QLQ-C30	95	55.7	Not specified	Not specified	Moderate
Villalta Cordova [16]	2016	Ecuador	EORTC QLQ-C30	40	50.4	I–II and III	Not specified	Moderate
Doubova [17]	2018	Mexico	EORTC QLQ-C30	136	53.6	Not specified	Not specified	Low
Hernández Moreno [18]	2014	Mexico	EORTC QLQ-C30	50	48.7	Not specified	Not specified	Low
Barber [19]	2018	Argentina	EORTC QLQ-C30 and B23	171	51.0	I–II and III	No	Moderate
Bevacqua [20]	2016	Argentina	EORTC QLQ-C30 and B23	100	61.8	I–II and III	No	Moderate
Costa [21]	2017	Brazil	EORTC QLQ-C30 and B23	400	Not specified	All	Yes	Moderate
Paiva [22]	2016	Brazil	EORTC QLQ-C30 and B23	153	51.9	I–II and III	No	Moderate
Castellar [23]	2014	Brazil	EORTC QLQ-C30 and B23	75	54.4	I–II and III	Not specified	Moderate
De Aguiar [24]	2014	Brazil	EORTC QLQ-C30 and B23	544	59.1	I–II and III	No	Moderate
Evangelista [25]	2012	Brazil	EORTC QLQ-C30 and B23	354	51.7	I–II and III	No	High
Ferreira [26]	2011	Brazil	EORTC QLQ-C30 and B23	195	58.2	I–II and III	No	High
Garcia [27]	2017	Brazil	EORTC QLQ-C30 and B23	48	46.0	I–II and III	No	Low
Michels [28]	2013	Brazil	EORTC QLQ-C30 and B23	100	56.5	I–II and III	Not specified	Low
Silva [29]	2013	Brazil	EORTC QLQ-C30 and B23	28	52.0	I–II and III	Yes	High
Lanza [30]	2015	Brazil	EORTC QLQ-C30 and B23	57	62.9	Not specified	No	Moderate
Dell'Antonio [31]	2017	Brazil	EORTC QLQ-C30 and B23	87	55.5	Not specified	Yes	Low
Gozzo [32]	2013	Brazil	EORTC QLQ-C30 and B23	48	48.4	Not specified	Yes	Moderate
Lobo [33]	2013	Brazil	EORTC QLQ-C30 and B23	145	52.0	Not specified	Yes	High
Velloso [34]	2011	Brazil	EORTC QLQ-C30 and B23	45	58.9	Not specified	No	High
Alfano [35]	2014	Brazil	EORTC QLQ-C30 and B23	126	51.4	Only metastatic disease	Yes	High
Irarrázaval [36]	2016	Chile	EORTC QLQ-C30 and B23	91	60.0	I–II and III	No	Moderate
Ardila Rojas [37]	2017	Colombia	EORTC QLQ-C30 and B23	362	55.7	Not specified	No	Moderate
Cortes-Flores [38]	2014	Mexico	EORTC QLQ-C30 and B23	139	49.7	All[a]	No	Moderate
Enríquez Reyna [39]	2018	Mexico	EORTC QLQ-C30 and B23	95	55.0	All[a]	Yes	Moderate
Sat-Muñoz [40]	2011	Mexico	EORTC QLQ-C30 and B23	314	52.2	All	Yes	Moderate
Gomez-Rico [41]	2009	Mexico	EORTC QLQ-C30 and B23	102	51.8	I and II	Yes	Moderate
Cerezo [42]	2012	Mexico	EORTC QLQ-C30 and B23	234	59.6	I–II and III	Yes	High

(continued)

Table 1. (continued)

Author	Year	Country	Instrument	Participants	Mean age (yr)	Cancer stage included	Patients in active treatment	Quality assessment
Recalde [43]	2012	Paraguay	EORTC QLQ-C30 and B23	125	55.0	All[a]	Yes	Moderate
Soto-Cáceres Cabanillas [44]	2013	Peru	EORTC QLQ-C30 and B23	76	Not specified	I–II and III	Not specified	Moderate
Sanchez-Pedraza [45]	2012	Colombia	FACT-B	198	54.2	All	Yes	Moderate
Bezerra [46]	2013	Brazil	FACT-B	197	53.0	I–II and III	Not specified	High
Baigorri [47]	2015	Argentina	FACT-B	156	60.7	I–II and III	No	Moderate
Fernandez-Suarez [48]	2010	Mexico	FACT-B	142	55.0	All	Not specified	
Pinto e Silva [49]	2008	Brazil	FACT-B	89	55.5	I and II	Yes	High
Oliveira [50]	2010	Brazil	FACT-B	55	52.7	Not specified[a]	Not specified	Moderate
Recchia [51]	2017	Brazil	FACT-B	30	51.2	I–II and III	No	High
Verde [52]	2009	Brazil	FACT-B	25	46.0	I and II	Yes	High
Perroud [53]	2016	Argentina	FACT-B	20	57.0	Only metastatic disease	Yes	High
Hundelhausen [54]	2015	Colombia	SF-36	50	55.0	Not specified[a]	No	Moderate
Reich [55]	2011	Uruguay	SF-36	116	50.8	All[a]	No	High
Lostaunau [56]	2013	Peru	SF-36	53	48.1	I–II and III	Yes	High
Palacios Benzaquen [57]	2014	Peru	SF-36	100	56.2	Not specified[a]	No	High
Soares [58]	2013	Brazil	SF-36	70	55.4	All[a]	No	High
Rancatti [59]	2013	Argentina	SF-36	221	52.0	I and II	No	High
Tiezzi [60]	2017	Brazil	SF-36	112	49.4	I–II and III	No	High
Manganiello [61]	2011	Brazil	SF-36	100	48.5	I–II and III	No	Moderate
Veiga [62]	2010	Brazil	SF-36	96	51.7	I–II and III	No	Moderate
Veiga [63]	2010	Brazil	SF-36	87	49.9	I–II and III	No	Moderate
Freitas-Silva [64]	2010	Brazil	SF-36	70	49.2	I–II and III	No	High
Simeao [65]	2013	Brazil	SF-36	50	57.2	I–II and III	No	Moderate
Tolentino [66]	2010	Brazil	SF-36	22	48.8	I–II and III	No	High
Trejo-Ochoa [67]	2013	Mexico	SF-36	74	48.4	I–II and III[a]	Yes	Moderate
Fontes [68]	2017	Brazil	SF-36	135	48.5	Not specified[a]	No	High
Medina [69]	2010	Mexico	SF-36	125	54.0	Not specified[a]	Not specified	Moderate
Mendes [70]	2014	Brazil	SF-36	49	53.9	Not specified[a]	No	Moderate
Oliveira [71]	2014	Brazil	SF-36 + WHOQOL-Bref + FACT-B	106	49.2	All[a]	No	High
Aguirre-Loaiza [72]	2016	Colombia	SF-36 + FACT-B	39	56.2	All	Not specified	Moderate
Binotto [73]	2016	Brazil	WHOQOL-Bref	272	58.5	All[a]	Yes	Moderate
Canario [74]	2016	Brazil	WHOQOL-Bref	215	52.7	All[a]	Yes	Moderate

(continued)

Table 1. (continued)

Author	Year	Country	Instrument	Participants	Mean age (yr)	Cancer stage included	Patients in active treatment	Quality assessment
Kluthcovsky [75]	2015	Brazil	WHOQOL-Bref	202	54.5	I–II and III	No	High
Rabin [76]	2008	Brazil	WHOQOL-Bref	73	47.9	I–II and III	No	High
Porciúncula Frenzel [77]	2013	Brazil	WHOQOL-Bref	70	55.6	I–II and III	Yes	Moderate
Seidel [78]	2017	Brazil	WHOQOL-Bref	58	51.6	Not specified[a]	Not specified	Moderate
Araújo Neto [79]	2017	Brazil	WHOQOL-Bref	50	54.0	Not specified	No	Moderate
Gomes [80]	2015	Brazil	WHOQOL-Bref	37	56.1	Not specified	No	Moderate
Elias [81]	2015	Brazil	WHOQOL-Bref	26	52.5	I–II and III	Not specified	Low
Santos [82]	2010	Brazil	WHOQOL-Bref	25	50.4	All[a]	Yes	Moderate
Zapata [83]	2010	Colombia	WHOQOL-Bref	220	53.5	Not specified	No	High
Pineda-Higuita [84]	2017	Colombia	WHOQOL-Bref	82	57.8	Not specified	Not specified	Moderate
Álviz Amador [85]	2016	Colombia	WHOQOL-Bref	23	50.2	Not specified	Not specified	Moderate

[a] These studies did not specify stage of disease but, according to study protocol or distribution of included patients, were assumed to represent patients in stages I, II, and III.

Abbreviations: EORTC QLQ, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; FACT-B, Functional Assessment of Cancer Therapy – Breast; SF-36, Short Form 36-item; WHOQOL-Bref, abbreviated version of the World Health Organization Quality of Life.

HRQoL with the WHOQOL-Bref Instrument

Of the 75 studies included in the systematic review, HRQoL was assessed by the abbreviated version of the World Health Organization Quality of Life (WHOQOL-Bref) instrument in 14 studies (two countries; *n* = 1,459). All the studies were carried out in two countries, and most of them were from Brazil (*n* = 11, *n* = 1,134). Sample sizes ranged from 23 to 273 patients, and the average age of participants from 47.9 to 57.8 years. Only 28% of the studies (4/14) were judged as high quality, whereas the rest were rated as moderate and only one as low quality. The score ranged from 5 to 9 points with a mean quality score of 6.85. The overall mean for domains in all populations ranged between 59.8 and 63.7 (Table 4). No studies have individually reported HRQoL of women with metastatic disease stages with the WHOQOL-Bref instrument. So, these results are mostly representative of the Brazilian population with stage I, II, or III disease because most of the sample came from this country and the distribution of patient subgroup could not be determined in the Colombian studies.

Supplemental online Table 3A–3D shows the comparative HRQoL measured by the different instruments (SF-36, QLQ-C30, QLQ-B23, and FACT-B) by country and disease stage. It can be shown, for example, that for SF-36, most studies were performed in mild to moderate disease, and only one Colombian paper includes women with stage IV disease. The physical functioning domain seemed to have a higher average for Argentina, as did the social functioning and emotional role ones. This same pattern was observed in most countries, albeit at different levels; notably, Colombian women scored lower among most countries. Additional details are shown in the abovementioned supplement.

Meta-Analysis of Conceptually Common Domains Across the Different HRQoL Instruments

In a further analysis, we reviewed the grammatical and conceptual structure of the multiple instruments to identify those conceptually equivalent domains with the objective of carrying out a pooled analysis. The specified analysis yielded seven conceptually similar domains. Table 5 shows the instruments included and the domains identified as conceptually equivalent.

The reported HRQoL scores of all domains were converted to a positive unified scale of 0–100, in which 0 is the worst possible score in each particular domain of each particular instrument and 100 the best possible score. In a similar manner to previous analyses, we performed a global analysis, as well as another one according to the stage of the disease. Table 6 shows the overall results and the subgroup analyses performed by stage and treatment.

In these pooled analyses of common domains, more patients were included with gains in statistical precision. We found, as compared with patients in follow-up and no active treatment, lower values in all domains of HRQoL of patients in active treatment (I, II, and III) and metastatic disease.

Table 2. Distribution of patients broken down by countries and instruments

Country	Patients, *n* (%)	EORTC QLQ-C30 and B23 (55.3%)	FACT-B (10.4%)	SF-36 (17.8%)	WHOQOL-Bref (16.6%)
Argentina	740 (8)	343	176	221	—
Brazil	4,963 (56)	2,642	396	791	1,134
Colombia	1,069 (12)	457	198	89	325
Mexico	1,411 (16)	1,070	142	199	—
Other	623 (7)	354	—	269	—
Total	8,806 (100)	4,866	912	1,569	1,459

Abbreviations: —, No studies found; EORTC QLQ, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; FACT-B, Functional Assessment of Cancer Therapy – Breast; SF-36, Short Form 36-item; WHOQOL-Bref, abbreviated version of the World Health Organization Quality of Life.

Table 3. Meta-analysis of health-related quality of life by EORTC QLQ-C30 and B23 domains broken down by stage of the disease and treatment

		Stages I, II, and III		
Domains	**Global**	**Active treatment**	**Follow-up**	**Stage IV**
EORTC QLQ-C30				
No. of studies (no. of patients)	34 (4,866)	14 (1,534)	12 (2,419)	3 (295)
Global health status	70.5 (68.2–72.7)	67.1 (64.6–69.5)	73.3 (69.5–77.2)	64.9 (56.4–73.3)
Physical functioning	74.5 (70.6–78.4)	75.7 (71.9–79.6)	81 (77.8–84.6)	64.8 (60.4–69.2)
Role functioning	67.2 (60.4–74.1)	60.2 (52.8–67.6)	81.8 (76.4–87.1)	56.3 (38.7–73.8)
Emotional functioning	63.2 (60.5–65.9)	65.2 (62.5–68)	65.5 (61.2–69.9)	57.4 (52.7–62.1)
Cognitive functioning	74.2 (69–79.4)	81.5 (76.9–86.1)	72.5 (67.6–77.4)	73.8 (64.6–83)
Social functioning	76.3 (69.7–82.9)	76.1 (67.5–84.8)	86.7 (85.1–88.3)	82.1 (79.2–84.9)
Fatigue	31.4 (25.1–37.6)	27.3 (23.7–30.8)	21 (18–24.1)	34.7 (31.1–38.4)
Nausea and vomiting	22.5 (17–28)	29.1 (25.2–33)	20.4 (16.7–24.1)	29.4 (21 – 37.8)
Pain	31.2 (27.8–34.6)	14.7 (10.3–19.1)	6.6 (4.6–8.5)	22.5 (13.8–31.3)
Dyspnea	21.6 (18–25.3)	7.5 (6.1–8.9)	11 (9.7–12.3)	29.4 (21–37.9)
Insomnia	34.5 (28.6–40.3)	28.4 (25.5–31.3)	28.7 (25.7–31.7)	34.3 (30.7–38)
Appetite loss	25.3 (21.3–29.3)	14.2 (12.9–15.5)	10.2 (8.2–12.3)	30 (21.5–38.5)
Constipation	27.6 (21.6–33.7)	14.3 (11.7–16.9)	17.6 (14.2–20.9)	29.8 (19.9–39.6)
Diarrhea	21.6 (15.9–23.6)	6.8 (5.1–8.4)	5.3 (4.4–6.2)	18.7 (10.5–26.9)
Financial difficulties	37.2 (29.3–45)	32.6 (27–38.2)	18.8 (16.4–21.1)	36.8 (27.8–45.8)
EORTC QLQ-B23				
No. of studies (no. of patients)	25 (4,342)	11 (1,435)	12 (2,032)	3 (295)
Body image	72.3 (59.6–85)	70.3 (54.4–86.2)	75.9 (62.7–89.3)	82.4 (73.8–91.1)
Sexual enjoyment	45.7 (38–53.4)	41.3 (31.9–50.7)	48.4 (35.8–61.1)	43.7 (21.6–65.8)
Sexual functioning	45.2 (31.9–58.5)	18 (16.6–19.4)	59.9 (45.0–74.8)	49.2 (20.8–77.7)
Future perspective	50.6 (40.5–60.8)	50.2 (37.5–62.9)	49.5 (35.1–63.9)	18.4 (13.1–23.7)
Arm symptoms	30.5 (26.4–34.6)	30.3 (26.0–34.6)	20.1 (17.6–22.5)	22.3 (20.6–23.8)
Breast symptoms	31.7 (24.7–38.7)	33.5 (15.7–51.4)	16.9 (14.5–19.4)	16.8 (15.5–18.1)
Systemic therapy side effects	33.9 (28.1–39.6)	36.2 (29.1–43.4)	21.5 (18.6–24.5)	25.5 (23.5–27.6)
Upset by hair loss	44.7 (34.5–54.9)	49.1 (34.2–63.9)	33.6 (22.4–64.8)	29.3 (20.9–37.7)

Data are shown as mean (95% confidence interval).
Abbreviation: EORTC QLQ, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire.

Discussion

The present study provides the most exhaustive analysis and synthesis to date of a heterogeneous body of evidence of breast cancer HRQoL in LAC.

We found 75 studies reporting HRQoL. Brazil was the most represented country. The EORTC QLQ-C30 questionnaire and the B23 module (disease-specific instruments) were the most commonly used tools. Most of them

Table 4. Meta-analysis of HRQoL by SF-36, FACT-B, and the WHOQOL-Bref instrument broken down by stage of the disease and treatment

		Stages I, II, and III		
Domains	**Global**	**Active treatment**	**Follow-up**	**Stage IV**
SF-36				
No. of studies (no. of patients)	19 (1,675)	2 (127)	15 (1,384)	1 (4)
Physical functioning	67 (62.8–71.2)	77.8 (56.7–98.9)	71.3 (67–75.5)	20.8 (8.3–33.3)
Role physical	48.4 (34.9–61.9)	51.4 (39.3–63.5)	51.9 (35.3–68.6)	12.5 (0–37)
Bodily pain	59.7 (54.2–65.3)	76.3 (67.4–85.2)	60.1 (53.6–66.7)	38.6 (3.5–73.7)
General health	67.6 (64.9–70.3)	68.2 (64–72.5)	69.1 (66–72.2)	38.7 (11.5–65.9)
Vitality	63.8 (61.2–66.4)	72.3 (67.9–76.8)	64.1 (61.1–67.1)	39.5 (6.7–72.3)
Social functioning	72.7 (67.3–78.0)	79.7 (67.1–92.2)	78.3 (74.6–82)	45 (40.6–49.4)
Role emotional	61.8 (53.5–70.2)	64.3 (58.9–69.8)	67.5 (56.3–78.8)	20.8 (0–45.3)
Mental health	68.3 (66.2–70.3)	69.7 (62.4–77)	69.3 (66.9–71.6)	45 (14.3–75.7)
FACT-B				
No. of studies (no. of patients)	11 (1,057)	6 (529)	2 (186)	2 (24)
Physical well-being	20.8 (19.4–22.2)	21.2 (19.8–22.6)	17.5 (15.3–19.7)	14.9 (6.5–23.4)
Social/family well-being	19.4 (17.7–21.2)	18.3 (15.6–20.9)	21.8 (18.6–24.9)	13.9 (2.1–25.8)
Emotional well-being	17.2 (14.9–19.5)	17.5 (16.3–18.7)	11.8 (8–15.6)	10.2 (8.1–12.4)
Functional well-being	18.9 (17.2–20.6)	17.9 (17.1–18.8)	21 (17–24.9)	12.7 (9.8–15.6)
Breast cancer subscale	23.1 (20.6–25.5)	23.6 (22.3–24.8)	16.1 (14–18.2)	23.7 (13.1–34.3)
WHOQOL-Bref[a]				
No. of studies (no. of patients)	13 (1,436)	4 (607)	5 (333)	—
Global HRQoL	67.3 (59.8–74.8)[a]	69 (58.9–79.1)	NR	NR
Satisfaction with health	67.9 (57.8–77.9)[b]	NR	NR	NR
Physical health	59.8 (57.0–62.7)	61.4 (56.8–65.9)	59.2 (54.2–64.1)	NR
Psychological	65.4 (61.4–69.3)	63.8 (56.4–71.2)	67.6 (62.6–72.6)	NR
Social relationships	66.7 (60.9–72.4)	68.9 (59.5–78.4)	70.8 (65.4–76.2)	NR
Environment	63.7 (61.2–66.4)	62.2 (58.2–66.3)	61.5 (56.7–66.3)	NR

Data are shown as mean (95% confidence interval).

[a] Only six studies (n = 713) report this domain.

[b] Only two studies (n = 95) report this domain.

Abbreviations: —, no equivalent domain was identified; FACT-B, Functional Assessment of Cancer Therapy – Breast; HRQoL, health-related quality of life; NR, not reported by any of the included studies; SF-36, Short Form 36-item; WHOQOL-Bref, abbreviated version of the World Health Organization Quality of Life.

Table 5. Conceptually equivalent domains of the instruments

EORTC QLQ-C30	**SF-36**	**FACT-B**	**WHOQOL-Bref**
Global health status	General health	—	Global HRQoL
Physical functioning	Physical functioning	Functional well-being	Physical health
Role functioning	Role physical	—	—
Emotional functioning	Role emotional	Emotional well-being	Psychological
Social functioning	Social functioning	Social/family well-being	Social relationships
Pain	Bodily pain	—	—

Abbreviations: —, No equivalent domain was identified; EORTC QLQ, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; FACT-B, Functional Assessment of Cancer Therapy – Breast; HRQoL, health-related quality of life; SF-36, Short Form 36-item; WHOQOL-Bref, abbreviated version of the World Health Organization Quality of Life.

measured HRQoL in early (I and II) and locally advanced (III) stages. Other frequently used instruments were generic instruments, such as the SF-36 and WHOQOL. We did not find studies that assessed HRQoL for other subgroups of interest, such as women with HER2-positive breast cancer. Using the random-effects model, we estimated that patients with a diagnosis of BC in active treatment or with metastatic disease had worse HRQoL in follow-up compared with survivors.

Several studies tried to characterize HRQoL in patients with breast cancer in whole countries or regions. A systematic review with meta-analyses in patients with cancer from

Table 6. Results of the joint analysis of the conceptually equivalent domains according to stage and phase of treatment

			Stages I, II, and III		
Domains		**Global**	**Active treatment**	**Follow-up**	**Stage IV**
Global	No. of studies (no. of patients)	59 (7,529)	18 (2,089)	26 (3,782)	3 (295)
	Mean (95% CI)	67.7 (62.6–72.7)	67.7 (65.1–70.3)	69.4 (51.1–79.6)	64.9 (56.3–73.4)
Physical	No. of studies (no. of patients)	69 (8,843)	22 (2,436)	28 (3,659)	5 (319)
	Mean (95% CI)	69.9 (67.6–72.2)	70.8 (65.5–75.2)	74.9 (72.4–77.3)	64.9 (56.3–73.4)
Emotional	No. of studies (no. of patients)	68 (8,615)	22 (2,416)	29 (4,192)	5 (319)
	Mean (95% CI)	65.4 (62.4–68.5)	65.8 (60.7–71)	66.7 (61.9–71.5)	54.9 (49.3–60.7)
Social	No. of studies (no. of patients)	68 (8,441)	24 (2,552)	30 (4,358)	5 (319)
	Mean (95% CI)	72.8 (69.2–76.3)	71.0 (64.7–77.3)	80.9 (78.3–83.5)	74.1 (64.6–83.6)
Role	No. of studies (no. of patients)	47 (6,672)	13 (1,362)	25 (3,697)	4 (299)
	Mean (95% CI)	60.8 (55.8–65.8)	54.3 (45.7–62.9)	65.1 (56.2 – 74.0)	49.7 (32.7–66.8)
Pain	No. of studies (no. of patients)	42 (5,782)	5 (872)	11 (2,216)	4 (177)
	Mean (95% CI)	66.9 (65.3–68.6)	72.9 (69–76.8)	67.2 (63.5–70.8)	47.9 (31.7–64.2)

Abbreviations: CI, confidence interval.

the Eastern Mediterranean region included 36 studies from 12 countries totaling 8,347 patients from 2008 to 2018 [86]. The most frequent instrument was the EORTC QLQ-C30 (20 studies; *n* = 6,043). The mean score of the global HRQoL ranged between 31.1 and 75.6. Based on the results of the random-effects method, the mean overall was 60.5. Comparisons show that the mean score of global HRQoL domains of this study are lower, indicating better QoL in LAC. The comparison of values in other domains shows very similar results.

A systematic review about HRQoL in women with breast cancer was performed in Spain, searching from 1993 to 2009 [88]. They identified 25 studies encompassing 2,236 women. In descending order of frequency, the questionnaires we used were the EORTC, FACT-B, Fonts' quality of life questionnaire, SF-12, Functional living index questionnaire, Rotterdam Symptom Checklist, and Quality of life Questionnaire. Most studies examined HRQoL according to the type of treatment. Few differences were detected by type of chemotherapy, with the single exception of worse results among younger women treated with radiotherapy. In the short term, better results were reported for all HRQoL components by women undergoing conservative rather than radical surgery. The presence of lymphedema was associated with worse HRQoL. Psychosocial disorder and level of depression and anxiety, regardless of treatment or disease stage, worsened HRQoL.

Compared with the EORTC-C30 reference values of 2008 for all stages of breast cancer, the mean scores of our study are slightly lower in most scales, indicating worse HRQoL in LAC [89]. However, the global health/QoL mean score in LAC was better than normative scores (70.5 vs. 61.8). Comparison of global health/QoL mean score between active treatment and follow-up stage subsets with reference values shows the same difference (67.1 and 73.3 vs. 61.8). One possible explanation for the differences observed is that reference values are based on pretreatment HRQoL data and patients who are off treatment were not included.

Our study is the first systematic review, to our knowledge, that focuses on BC in LAC. Some limitations might undermine our findings. Even though we had a very sensitive search strategy for all countries, that incorporated traditional databases, gray literature, reference identification, and experts, we found studies in only 9 of the 46 LAC countries. Also, study quality was heterogeneous: participation and response rates for patient groups were not described in a significant percentage of the studies, and selection bias was present in most of studies, which may hamper internal validity and, ultimately, generalizability. Lastly, most studies did not report key clinical variables that could influence HRQoL, such as average time since diagnosis, last treatment performed, or the exact moment in which HRQoL was measured in the patients with BC. HRQoL is a dynamic multidimensional measurement. All the aforementioned factors could partly explain the very high heterogeneity found in the main results, thus calling for caution in the interpretation of pooled results. This substantial level of heterogeneity is commonly found in epidemiological systematic reviews including different countries, and a meaningful way to address it is by bringing more attention to the range of uncertainty around them (i.e., 95% confidence intervals).

Comparison of limited versus diffuse disease, or early stages in follow-up versus active treatment, showed significantly worse HRQoL scores in the last groups with an important limitation when performing this analysis. Of note, there was only a handful of studies (in four countries; total *n* = 315) that reported detailed data from patients with metastatic disease. In a large proportion of included studies, the precise stage of the disease was not determined, or women belonged to a mix of stages, which prevented knowing specific HRQoL data without access and reanalysis of the primary data. It is reasonable to expect changes throughout the continuum of care of the disease. Owing to the short time frame of the questionnaires (ranging from 1 to 4 weeks), the inability to temporarily relate the measured quality of life to an exact moment of the continuum of care is another significant limitation of the studies included. Another aspect that could not be well informed by our results relates to the longitudinal changes in HRQoL in these patients along the natural history of breast cancer. There were no longitudinal studies assessing this aspect, and our analysis mainly focuses on cross-sectional analysis and comparisons of predefined patient populations. All these limitations of external validity were also generally found in the aforementioned systematic reviews that assessed HRQoL in BC and thus must be interpreted with caution.

Our study did not focus on the comparative validity of the different instruments in different populations and contexts, so prospective researchers do not have a straightforward solution on which instrument to include in a study. Their choice should be based partly on the instrument dissemination and validity evidence in their setting; their main research interest (i.e., choose a specific instrument such as the EORTC QLQ-C30 or a generic one that can help compare the HRQoL impact in this population of patients with other health conditions); or specific domains of interest (instruments usually share selected dimensions but also have domains that are not present in other potential instruments; see Table 5 for clarification of this aspect).

Our results also expose important evidence gaps. Additional research is needed to better report HRQoL in the future in clearly defined patient subgroups to determine HRQoL of women with metastatic disease or in other subgroups such as those that present overexpression of the HER2/neu gene. Economic evaluations are an increasingly important component in making decisions about the inclusion of treatments and resource allocation in benefits packages, and HRQoL is a key component. The reference values provided from our study can be used to derive quality-adjusted life years and improve health decision making in Latin America.

CONCLUSION

This study provides an exhaustive analysis and synthesis of a body of evidence of BC HRQoL in LAC and gives reference values averaged across nine countries. The research published was mainly from Brazil, followed by Mexico and Colombia. We summarized existing evidence and its inherent uncertainty by countries and patient subgroups, also exposing the existence of evidence gaps. Estimates should be interpreted with caution owing to important heterogeneity and selection bias. Our results also signal research priorities in LAC, such as better reporting, and conducting future HRQoL studies, studying it in women with metastatic disease or different relevant subgroups such as those that present overexpression of the HER2/neu gene.

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DISCLOSURES

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