Health-Related Quality of Life of Breast Cancer Patients: Integrative Literature Review

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Qualidade de Vida Relacionada à Saúde de Pacientes com Câncer de Mama: Revisão Integrativa da Literatura
Calidad de Vida Relacionada con la Salud de Pacientes con Cáncer de Mama: Revisión Integradora de la Literatura

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Abstract

Introduction: Breast cancer can change the health-related quality of life of patients. **Objective:** To understand the impact of chemotherapy for breast cancer on the health-related quality of life of patients. **Method:** Integrative review of the literature, comprising articles published between 2007 and 2019, available in PubMed, LILACS and SciELO databases. It were analyzed 25 articles. **Results:** The questionnaires most frequently used in the studies were the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) and the European Organization for Research and Treatment of Cancer Breast Cancer-specific Quality of Life Questionnaire (EORTC QLQ-BR23) complementary module. In relation to changes in the quality of life, the global health diminishes during chemotherapy, but may improve after the end of the treatment. The increase of the symptoms is reported in several studies and have impaired the patients' health-related quality of life. However, symptoms decrease after chemotherapy ends, except in some scales. Body image, sexual function and physical functioning scales get worse throughout the treatment. Mental/psychological quality of life has oscillations during treatment, as does the scale on social relationships. **Conclusion:** The health-related quality of life of women with breast cancer is negatively affected by chemotherapy treatment, causing major impact in the scales of symptoms.

Key words: Quality of Life; Surveys and Questionnaires; Breast Neoplasms; Drug Therapy.

Resumo

Introdução: O câncer de mama pode alterar a qualidade de vida relacionada à saúde das pacientes. **Objetivo:** Compreender o impacto da quimioterapia para câncer de mama na qualidade de vida relacionada à saúde de pacientes. **Método:** Trata-se de uma revisão integrativa da literatura, compreendendo artigos publicados entre 2007 e 2019, disponíveis nas bases de dados PubMed, LILACS e SciELO. Analisaram--se 25 artigos na íntegra. **Resultados:** Os questionários mais frequentemente utilizados nos estudos foram o *European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire* (EORTC QLQ-C30) e o módulo complementar *European Organization for Research and Treatment of Cancer Breast Cancer-specific Quality of Life Questionnaire* (EORTC QLQ-BR23). Em relação às alterações da qualidade de vida, a saúde global diminui durante a quimioterapia, mas pode melhorar após o término do tratamento. O aumento dos sintomas é relatado em diversos estudos e prejudicou a qualidade de vida relacionada à saúde das pacientes. Entretanto, os sintomas diminuem após o término da quimioterapia, exceto para algumas escalas. As escalas de imagem corporal, função sexual e funcionamento físico pioram ao longo do tratamento. A qualidade de vida mental/psicológica tem oscilações durante o tratamento, assim como a escala sobre as relações sociais. **Conclusão:** A qualidade de vida relacionada à saúde de mulheres com câncer de mama é afetada negativamente pelo tratamento quimioterápico, expressando maior impacto nas escalas de sintomas.

Palavras-chave: Qualidade de Vida; Inquéritos e Questionários; Neoplasias da Mama; Tratamento Farmacológico.

Resumen

Introducción: El cáncer de mama puede alterar la calidad de vida relacionada con la salud de las pacientes. **Objetivo:** Comprender el impacto de la quimioterapia para el cáncer de mama en la calidad de vida relacionado con la salud de los pacientes. **Método:** Es una revisión integradora de la literatura, que comprende artículos publicados entre 2007 y 2019, disponibles en las bases de datos PubMed, LILACS y SciELO. Se analizaron 25 artículos en su totalidad. **Resultados:** Los cuestionarios más utilizados fueron *European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire* (EORTC QLQ-C30) y *European Organization for Research and Treatment of Cancer Breast Cancer-specific Quality of Life Questionnaire* (EORTC QLQ-BR23). Con respecto a los cambios en la calidad de vida, la salud general disminuye durante la quimioterapia, pero puede mejorar después del final del tratamiento. El aumento de los síntomas se informa en varios estudios y afecta la calidad de vida relacionado con la salud de los pacientes. Sin embargo, los síntomas disminuyen después de que termina la quimioterapia, excepto en algunas escalas. Las escalas de imagen corporal, la función sexual y la función física empeoran a lo largo del tratamiento. La calidad de vida mental/psicológica tiene oscilaciones durante el tratamiento, al igual que la escala en las relaciones sociales. **Conclusión:** La calidad de vida relacionada con la salud de las mujeres con cáncer de mama se ve afectada negativamente por el tratamiento quimioterapéutico, que expresa un mayor impacto en las escalas de los síntomas.

Palabras clave: Calidad de Vida; Encuestas y Cuestionarios; Neoplasias de la Mama; Quimioterapia.

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INTRODUÇÃO

Breast cancer is the most incident tumor and with higher mortality in women in the worldwide[1,2]. The development of breast cancer has a multifactorial etiology and may involve biological and endocrine factors related to the reproductive life, behavior and lifestyle. The most known risk factors are aging, early menarche, late menopause, nulliparity or advanced age in the pregnancy of the first child, prolonged use of oral contraceptives and/or hormone replacement at menopause, family history of breast cancer and high density of breast tissue[2,3]. In addition, there are genes that have been shown to be responsible for the hereditary nature of certain breast cancer as BRCA1 and BRCA2, in addition to ATM, PALB2, BRIP1, CHEK, BARD1, which, although they are less frequent genes, may also be responsible for the increased risk of breast cancer[4]. Finally, a sedentary lifestyle, excessive alcohol consumption and exposure to radiation ionizing agents are also considered potential agents for the development of this cancer[2,5].

Adjuvant systemic therapies are effective in reducing the risk of breast cancer recurrence, including endocrine therapy, anti-HER2 therapy and chemotherapy[6]. Neoadjuvant therapy for early breast cancer can make the setorectomy more feasible, with less physical impairment and psychological problems to the patient, in addition to possible clinical benefits. A recent meta-analysis compared the long-term outcomes between adjuvant and neoadjuvant treatments and concluded that breast cancer mortality rates are equivalent[7].

However, breast cancer treatment causes negative effects in the recovery and health-related quality of life (HRQoL) of the survivals[8]. Regardless of the curative intent of therapies, it is essential to analyze the questions about the effects related to long-term toxicity, which can affect the overall quality of the patient survival[9]. Thus, it is common to affirm that chemotherapy is the type of treatment that most negatively impacts the HRQoL of breast cancer patients[10].

The patients reported outcomes are even more included in the clinical studies, becoming important in the scientific literature. The increased inclusion of HRQoL analysis in clinical studies can be evidenced by the significant addition of this theme during the American Society of Clinical Oncology (ASCO) Annual Meeting. In a search on the electronic platform that provides the abstracts presented during the congress[11], there was an increase in the number of those addressing the topic in question, between the years 2014 and 2018. Thus, the number of abstracts published according to the term HRQoL increased from 89 abstracts in 2014 to 180 in 2018. The number of abstracts published according to the term quality of life (QoL) (which is the most comprehensive term related to the same subject) increased from 322 abstracts in 2014 to 410 abstracts in 2018.

Therefore, the objective of this study is to review the literature, to evaluate the impact of the chemotherapy treatment on HRQoL in patients with breast cancer. In addition, it was intended to identify which instruments are most frequently used to measure these changes.

METHOD

The method utilized was an integrative literature review. The guiding question was: "What is the impact of the chemotherapy treatment on the HRQoL of breast cancer patients?" To search the articles to be reviewed, the PubMed, LILACS and SciELO databases were used. Articles published during the period from 2007 to 2019 were identified, through descriptors in Portuguese (*qualidade de vida, neoplasias da mama, quimioterapia, tratamento farmacológico, quimioterapia farmacológica, quimioterapia combinada ou protocolos de quimioterapia combinada antineoplásica*) and the corresponding descriptors in English (Quality of Life, Breast Neoplasms, Drug Therapy, Chemotherapy Adjuvant, Chemotherapy Cancer, Regional Perfusion, Antineoplastic Combined Chemotherapy Protocols, Antineoplastic Agents, Drug Therapy Combination).

Eligibility criteria for selecting articles were considered: 1) that the patients were women; 2) who had breast cancer (regardless of clinical stage); 3) that the studies addressed chemotherapy for the treatment of breast cancer; 4) the studies have carried out an evaluation comparative of HRQoL in two or more moments of the chemotherapy treatment; 5) that the evaluation of the impact of chemotherapy was the main theme of the study. Opinion articles, editorials, case reports, letters to the editor and comments were excluded from the analysis. The complete list of the included and excluded articles is shown in Figure 1.

RESULTS

Eight different questionnaires for evaluation of HRQoL were used in the studies included in this review. Fourteen studies utilized the *European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire* (EORTC QLQ-C30)[12-25], but only nine studies utilized the complementary module for breast cancer *European Organization for Research and Treatment of Cancer Breast Cancer-specific Quality of Life Questionnaire* (EORTC QLQ-BR23)[12,17,18,20-25]. Six studies utilized the *Functional*

Assessment of Cancer Therapy – Breast (FACT-B)[19,25-29] questionnaire and two the *Functional Assessment of Cancer Therapy* – General (FACT-G)[30,31]. The *Medical Outcomes Study 36-item Short Form 36* (SF-36) questionnaire was used by three studies[32-34], as well as the *European Quality of Life 5 Dimensions* (EQ-5D)[16,28,35] questionnaire. Still, one study used the *Quality of Life Questionnaire for Cancer Patients Treated with Anti-Cancer Drugs* (QOL-ACD)[35] and another, the *International Breast Cancer Study Group Quality of Life Core Questionnaire* (IBCSG QL core)[36]. The most frequent study design was the longitudinal (n=10), followed by the cohort studies nested in randomized clinical trial (RCT) (n=6). The methodological synthesis of the articles is summarized in Table 1.

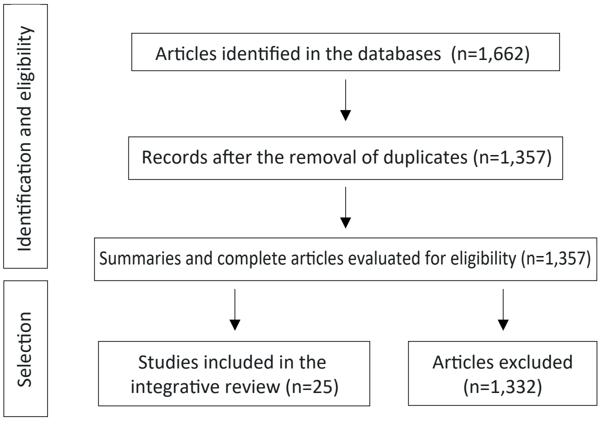

Figure 1. Flowchart for selecting articles from the integrative literature review

Regarding changes in HRQoL, global health decreased during chemotherapy[12,14,15,17-19,21,23,25], but can improve after the end of treatment[14,17,25,36]. In addition, global health can be negatively impacted due to adverse events caused by chemotherapy[16]. The increase in symptoms related to systemic therapy is reported in several studies[12,15,17-19,21,23,26,34] and impaired the patients' HRQoL. Among the studies that evaluated HRQoL in periods that

Table 1. Characterization of the studies analyzed during the integrative literature review

Author	N	Design	Objective	Questionnaires	Method of application of questionnaires	Chemotherapy
Au et al.[17]	3,222	RCT	Describe and compare HRQoL in patients with breast cancer in early stage	EORTC QLQ-C30 and EORTC QLQ-BR23	Baseline, early of the 4th. cycle, at the end of chemotherapy and 6, 12 and 24 months after chemotherapy	Adjuvant
Baena-Cañada et al.[12]	50	Cohort nested in RCT	Evaluate the effect of chemotherapy in HRQoL and in clinical variables	EORTC QLQ-C30 e EORTC QLQ-BR23	Before chemotherapy, midpoint of treatment and end of the treatment	Adjuvant
Bastani e Kiadaliri[13]	100	RCT	Compare the differences between the levels of HRQoL after receiving two protocols of chemotherapy	EORTC QLQ-C30	After the end of chemotherapy and 4 months after the end of chemotherapy treatment	Adjuvant
Berger et al.[33]	196	Cohort nested in RCT	Examine the relations among fatigue, physical and mental QoL in different protocols of chemotherapy	Piper Fatigue Scale and SF-36	48 hours before the treatment and 4, 8 and 30 days after the final treatment	Adjuvant
Bernhard et al.[36]	243	RCT	Evaluate HRQoL, toxicity and time without symptoms until death	IBCSG QL core	Before the start of treatment and at 3 6, 9, 12 and 18 months	Adjuvant
Browall et al.[18]	150	Longitudinal	Describe the changes of HRQoL during the treatment and identify the best predictors of global QoL after the treatment	EORTC QLQ-C30, EORTC QLQ-BR23 and HADS	Before the start of treatment, during and after complete treatment	Adjuvant
Cámara et al.[14]	3,691	Cohort nested in RCT	Compare the QoL before, during and up to one year after chemotherapy	EORTC QLQ-C30	Before the treatment, after the 3rd, 6th, 9th and 12th months	Adjuvant

to be continued

Table 1. continuation

Author	N	Design	Objective	Questionnaires	Method of application of questionnaires	Chemotherapy
Ganz et al.[26]	300	RCT	Compare the effect of treatments on QoL and menstrual history	FACT-B and FACT- TOI	Before the start of treatment, after the 4th. cycle and at every 6 months for up to 24 months of follow-up	Adjuvant
Gaton-Johansson et al.[19]	30	Longitudinal	Determine if there is a difference in intensity of symptoms and QoL during chemotherapy	EORTC QLQ-C30, FACT-B, HADS, ISI, POM and VAS	Before the start of treatment, midpoint of chemotherapy and one week after the conclusion of chemotherapy	NI
Gozzo et al.[20]	79	Longitudinal	Evaluate the HRQoL and identify the occurrence of nausea and vomiting during treatment	EORTC QLQ-C30 and EORTC QLQ-BR23	Before the start of treatment, at the midpoint and at the end of treatment	Adjuvant or neoadjuvant
Hagiwara et al.[16]	380	Cohort nested in RCT	Investigate the impact of adverse events on health utility and HRQoL in patients with metastatic breast cancer undergoing first-line chemotherapy.	EORTC QLQ-C30 and EQ-5D	At baseline, 3, 6 and 12 months after starting treatment	Adjuvant
Hall et al.[21]	830	RCT	Explore the profile of chemotherapy toxicity and the impact on HRQoL	EORTC QLQ-C30, EORTC QLQ-BR23 and HADS	At baseline, after cycles 4 and 8 of chemotherapy, at 9, 12, 18, 24 months and up to 6 years of follow-up	Adjuvant
Hatam et al.[15]	100	Longitudinal	Compare two chemotherapy regimens in breast cancer patients, analyze the toxicity of these treatments and observe HRQol.	EORTC QLQ-C30	During the first cycle of chemotherapy and after 4 months of follow-up	Adjuvant
Ho et al.[30]	269	Subanalysis of longitudinal study	Compare the psychological health and HRQoL and determine the relationship between anxiety, depression and QoL during and one year after of the end of treatment	FACT-G and HADS	During and after 1 year of treatment	Adjuvant
Huang et al.[34]	121	Longitudinal	Compare symptoms and QoL among patients who received target therapy, chemotherapy, or combined therapy.	SF-36	Before the treatment, 4 and 12 weeks after the start of treatment	NI
Klemp et al.[32]	20	Longitudinal	Examine changes in subjective and objective cognitive functions and on HRQoL, of women pre and perimenopause receiving chemotherapy for breast cancer, to explore potential predictors of cognitive changes	BCPT, BDI, BFI, CDS, FACT-COG, HSCS, MDASI and SF-36	Before chemotherapy, after cycle 3, within 2-3 weeks after adjuvant chemotherapy and more than 8 years later	Neoadjuvant and adjuvant

to be continued

Table 1. continuation

Author	N	Design	Objective	Questionnaires	Method of application of questionnaires	Chemotherapy
Kornblith et al.[22]	350	Subanalysis RCT	Evaluate if the treatment with capecitabine is associated with better HRQoL than standard chemotherapy	EORTC QLQ-C30, EORTC QLQ-BR23 and HADS	Before treatment, at the midpoint of treatment, after 1 month post-treatment and at 12, 18 and 24 months of follow-up	Adjuvant
Leinert et al.[23]	1,363	Subanalysis RCT	Compare HRQoL in patients receiving adjuvant chemotherapy	EORTC QLQ-C30 and EORTC QLQ-BR23	Before starting treatment, before the 4th or 5th cycle of chemotherapy, 4 weeks after chemotherapy and 6 weeks after radiotherapy	Adjuvant
Montazeri et al.[24]	167	Longitudinal	Examine the impact of the diagnosis and treatments on HRQoL	EORTC QLQ-C30 and EORTC QLQ-BR23	After the diagnosis of breast cancer, 3 months after the start of treatment and 1 year after the end of treatment (follow-up of 18 months)	Adjuvant
Perroud et al.[27]	20	Cohort nested in RCT	Identify changes in HRQoL during chemotherapy	BPI and FACT-B	Before the start of treatment, midpoint and at the end of treatment	Adjuvant
Sanford et al.[31]	80	Longitudinal	Observe sleep quality in breast cancer patients in adjuvant chemotherapy and evaluate its relationship with HRQoL	HADS, FACT-ES, FACT-F, FACT-G and PSQI	3-14 days before start of chemotherapy, in the 4th cycle of chemotherapy and 6 months after the start of chemotherapy	Adjuvant
Shiroiwa et al.[28]	299	Cohort nested in RCT	Analyze the HRQoL and the effect of adjuvant chemotherapy in patients on RCT	EQ-5D and FACT-B	Before the administration of chemotherapy in cycles 3, 5 and 7, after 7 months and 1 year after the start of chemotherapy	Adjuvant
Tachi et al.[35]	48	Longitudinal	Clarify the impact of adverse events associated with the initial course of outpatient chemotherapy in HRQoL	EQ-5D and QOL-ACD	Before and after the first cycle of chemotherapy	Adjuvant and neoadjuvant
Winters et al.[25]	182	Cohort	Evaluate if there are differences in HRQoL after immediate breast reconstruction	BIS, EORTC QLQ-C30 and EORTC QLQ-BR23, FACT-B and HADS	Before surgery and at 3, 6 and 12 months after surgery	Adjuvant and neoadjuvant
Zhang et al.[29]	88	Longitudinal	Investigate anxiety, depression and QoL during the different intermittent periods between chemotherapy	FACT-B, SAS and SDS	In the 2nd, 3rd, 4th, 5th and 6th cycles of therapy, always in the first day of the cycle	Adjuvant

Captions: BCPT: Cognitive Problems Scale from the Breast Cancer Prevention Trial; BDI: Beck Depression Inventory I; BFI: Brief Fatigue Inventory; BPI: Brief Pain Inventory; BIS: Body Image Scale; CDS: Cognitive Difficulties Scale; EORTC: European Organization for Research and Treatment of Cancer; EORTC QLQ-BR23: EORTC Breast Cancer-specific Quality of Life Questionnaire; EORTC QLQ-C30: EORTC Core Quality of Life Questionnaire; EQ-5D: European Quality of Life 5 Dimensions; FACT: Functional Assessment of Cancer Therapy; FACT-B: FACT Breast; FACT--COG: Functional Assessment for Cancer Therapy-Cognition; FACT-ES: FACT Endocrine Subscale; FACT-F: FACT Fatigue; FACT-G: FACT General; HADS: The Hospital Anxiety and Depression Scale; HRQoL: Health-related Quality of Life; HSCS: The High Sensitivity Cognitive Screen; IBCSG QL core: International Breast Cancer Study Group Quality of Life Core Questionnaire; ISI: The Insomnia Severity Index; MDASI: MD Anderson Symptom Inventory; NI: No information; POM: Pain-O-Meter; PSQI: Pittsburgh Sleep Quality Index; QOL-ACD: Quality of Life Questionnaire for Cancer Patients Treated with Anti-Cancer Drugs; QoL: Quality of Life; RCT: Randomized Clinical Trial; SAS: Self-rating Anxiety Scale; SDS: Self-rating Depression Scale; SF-36: Medical Outcomes Study 36-item Short Form; TOI: Trial Outcome Index; VAS: Visual Analogue Scale.

included post-treatment, most of them demonstrated that symptoms reduced after the end of chemotherapy[17,19,21,26], except for some scales such as depression, fatigue and interference of pain in the daily activities, whose scores may increase at the end of chemotherapy compared to the baseline[19]. Regarding the body image scale, the results worsened with the treatment[12,18,24]. Body image and sexual function were the HRQoL scales that presented the longest period for the recovery of scores at baseline levels[21], or that did not show recovery during the period evaluated[24]. Despite the physical functioning, scales of activity or physical condition decrease during chemotherapy[12,18,29,30,35], improvement in this scale was reported after the end of treatment in some studies[23,33,37]. However, post-treatment worsening was described in one of the studies[19].

Mental QoL, condition or psychological functioning, emotional or cognitive function (nomenclature differs depending on the questionnaire used) also indicated changes because of the treatment. During treatment, a reduction in mental QoL was identified, which improved after chemotherapy ended[32,33]. Other authors reported that the psychological/emotional function and cognitive functioning only increase after a certain period, at the end of treatment[13].

Regarding social support, the results differ depending on the study. While one study reports that the scale increases during treatment[35], others affirm that the scores decrease during treatment, but increase after the end[13,25]. And finally, there are those authors who believe that this scale worsens due to treatment[18,19,24,29]. Therefore, it is believed that the impacts on the social support scale differ depending on the degree of psychosocial adjustment of each patient. The summary of the results of each article is presented in Table 2.

DISCUSSION

Through the integrative literature review, it is perceived that, in most cases, chemotherapy is responsible for the

Table 2. Summary of the main results of the studies analyzed in the integrative review

Author and reference	Results
Au et al.[17]	Physical functioning was somewhat worse for those who received ACT compared to the group receiving TCH (p<0.002). At the midpoint, the TCH group was worse than the ACTH group (p=0.005), but similar between the arms with recovery at 12 months. The scores changes in the systemic side effect were better in patients treated with TCH in comparison with ACTH and ACT at the end of treatment (p=0.001), suggesting more tolerability. All treatment arms recovered for systemic side effect, physical and on the global health scale in 1 year and the mean scores of changes in perspective future continued to improve over the course of treatment and follow up.
Baena-Cañada et al.[12]	Global health status/QoL worsened along the time (p=0.01) while the scores of physical functioning (p=0.0001) and body image (p=0.002) had great negative impact with chemotherapy. There was an increase in the symptoms of systemic treatment (p=0.001). Some of them presented more negative and temporal impact of chemotherapy such as fatigue (p=0.004), loss of appetite (p=0.025), nausea and vomiting (p=0.05).
Bastani e Kiadaliri[13]	At the end of chemotherapy, HRQoL scores improved in all five aspects of the state of function (physical, functional, emotional, cognitive and social) and global health status/QoL in the both groups. In both arms, most progresses was observed in physical functioning (13% increase in FAC and 29% in TAC). At the end of chemotherapy, the mean score of HRQoL in the FAC group was higher than TAC (p<0.005).
Berger et al.[33]	Low physical QoL scores at the start of treatment (compared to control) and between 4th. and 8th. cycles, with improvement in 30 days after the end of chemotherapy. There was worsening physical QoL over time, regardless of the chemotherapy protocol (p<0.001). Mental QoL of the patients was initially like control, with decline after the 4th cycle, that only recovered in the 8th. cycle and in post-therapy. Mental QoL has been impacted over time, regardless of the chemotherapy protocol (p<0.001).
Bernhard et al.[36]	There were no baseline differences between treatments. There was a reduction of HRQoL during the treatment, with accentuated improvement 3 months after chemotherapy (in both groups). This recovery was greater and faster in DI-EC cohort, in comparison with SD-CT cohort. The change in coping scores after completion of therapy in the DI-EC arm improved from month 3 to 6 (p<0.01), while in the SD-CT arm, the coping score improved from month 6 until month 9 (p<0.01). The patients of DI-CE cohort obtained better health estimates throughout the follow-up.

to be continued

Table 2. continuation

Author and reference	Results
Browall et al.[18]	Decrease in global health scores/QoL, functioning (physical, social and cognitive), role functioning, body image and anxiety, in addition to increase of the scores of fatigue, nausea, vomiting, dyspnea, loss of appetite, constipation, pain, systemic therapy side effects measured, hair loss and depression (in comparison with baseline, 3rd and 6th chemotherapy cycles). At baseline, some scales were correlated with better general health/QoL at the end of the treatment: functional performance ($p<0.05$) and physical ($p<0.01$), emotional ($p<0.5$) and social ($p<0.5$) functioning, that is, as best at baseline, better were health general QoL in the end of chemotherapy. Relation inversely proportional for fatigue ($p<0.01$), depression ($p<0.05$) and anxiety ($p<0.05$).
Cámara et al.[14]	At all times, the mean global QoL was higher with FEC-DG than with FEC-D ($p=0.05$) and, in the 3rd. follow up, this difference reached its maximum of two points ($p=0.02$), but both results are below the threshold of clinical relevance. Women in FEC-DG group reported less pain and fatigue and physical function better in the 3rd. follow up ($p=0.001$).
Ganz et al.[26]	Time ($p<0.001$), chemotherapy treatment ($p<0.001$) and surgery/radiation combination ($p<0.024$) were predictors of change from baseline to 24 months of follow-up of HRQoL. Patients of the ACT group reduced the score of HRQoL in relation to the baseline (effect size 0.2), as well as the patients on AT (effect size 0.1). The time-for-treatment interaction demonstrated that the physical and functional well-being of the patients with TAC and AT returned to the baseline at 6 months, while of the patients with ACT returned to baseline at 12 months ($p<0.001$). The symptoms increased over the course of treatments, without returning to baseline levels.
Gaton--Johansson et al.[19]	Worsening of pain interference in daily activities ($p=0.001$), in addition to increased fatigue ($p<0.001$), nausea present ($p=0.005$), history of nausea ($p=0.006$) and insomnia ($p=0.024$) with chemotherapy. There was greater intensity of pain, nausea, history of fatigue and insomnia in the midpoint of chemotherapy. More depression, fatigue, and interference of pain in the daily activities post-therapy. Worsening of global health/QoL ($p=0.001$), physical well-being ($p<0.001$), functional ($p<0.001$) and familiar/social ($p=0.001$) throughout the treatment.
Gozzo et al.[20]	Overall, HRQoL remained stable during treatment. Exception for the greater presence of nausea and vomiting at least once, during the treatment: EC-T/EC-TH (beginning/middle -9.3746, $p=0.0118$ and beginning/end -9.1052, $p=0.0151$) and FEC (beginning/middle -18.2789, $p=0.0001$ and beginning/end -12.9026, $p=0.0055$).
Hagiwara et al.[16]	The negative impact of AE caused by chemotherapy on HRQoL was observed for grade 1 fatigue ($p=0.001$), grade 2 fatigue ($p=0.042$) and grade 1 oral mucositis ($p=0.040$). At the scales of functioning, there was compromise caused by grade 2 motor neuropathy (- 21.0; CI 95% - 25.4 to – 16.7) and grade 2 sensorial neuropathy (- 6.9; CI 95% - 12.3 to – 1.5) for physical functioning; grade 1 motor neuropathy (- 14.2; CI 95% - 26.3 to – 2.0), grade 1 and 2 fatigue (- 6.7 and – 6.8; CI 95% - 10.6 to – 2.9 and – 12.3 to – 1.4, respectively), and grade 2 myalgia (- 19.9; CI 95% - 36.8 to – 3.1) per function of roles; grade 1 fatigue (- 4.0; CI 95% - 7.4 to – 0.6) and grade 1 edema (- 4.8; CI 95% - 9.3 to – 0.2) for emotional functioning; grade 1 oral mucositis (- 6.2; CI 95% - 12.1 to – 0.2) for cognitive functioning; grade 1 nausea (- 5.9; CI 95% - 11.4 to – 0.5) and grade 1 edema (- 5.6; CI 95% - 11.1 to – 0.1) for social functioning.
Hall et al.[21]	Global health / QoL compromise between baseline and treatment: worse for the FEC-D group compared to controls in cycle 8 ($p<0.0001$). Recovery at baseline levels occurred in both protocols for 12 months, with scores unchanged from baseline values at 2 and 6 years. Increased systemic side effects in FEC-D from the beginning to the middle of treatment. In cycle 8, this increase was also significantly greater in patients with ($p=0.005$). All systemic effects (except xerostomia) reduced in post-treatment, but without returning to baseline. Body image and sexual functioning required more time to resolve. No additional changes were identified at 6 years.
Hatam et al.[15]	After the follow-up of the patients for 4 months, the results indicated that, despite having the same mean HRQoL score at the beginning of chemotherapy, HRQoL in the TAC group was worse, with more toxicity. HRQoL after the 1st. cycle of chemotherapy did not present differences between TAC or FAC, with similar mean score. At the end of chemotherapy, HRQoL in both groups deteriorated because of the side effects. However, the decrease was greater in the TAC group in all the aspects of the patient's functional status: physical function ($p=0.002$), functional ($p=0.006$), emotional ($p=0.007$), cognitive ($p=0.02$), social ($p=0.002$) and global health status/QoL ($p<0.001$).

to be continued

Table 2. continuation

Author and reference	Results
Ho et al.[30]	Lower levels of HRQoL during chemotherapy. Higher anxiety was associated with lower physical well-being (during treatment: beta -0.25 $p<0.001$, after: beta 0.21 $p=0.03$), emotional (during: beta -0.57 $p<0.001$, after beta -0.72 $p<0.001$) and functional (during: beta -0.21 $p=0.001$ and after: beta -0.32 $p<0.001$). Higher levels of depression were associated with lower physical well-being (during: beta -0.34, $p<0.001$, after; beta -0.37 $p<0.001$), social/familiar (during: beta -0.26 $p=0.001$, after: beta -0.34 $p=0.001$), emotional (only during the treatment: beta -0.22 $p<0.001$) and functional (during: beta -0.48 $p<0.001$, after: beta -0.43 $p<0.001$).
Huang et al.[34]	The severity of symptoms increased over time among the patients who received chemotherapy (mean: 26.2±15.5 for pre-treatment, 31.1±18.4 in the 4 weeks after starting treatment and 34.2±22.2 in the 12 weeks after starting treatment; $p=0.02$).
Klemp et al.[32]	Higher QoL was correlated with better subjective cognitive function ($r=0.705$, $p=0.002$) and lower body mass index ($r=-0.502$, $p=0.017$). The scores of the physical component of HRQoL improved along the time ($p=0.037$). There was no change in the score of the mental component.
Kornblith et al.[22]	Capecitabine-treated patients achieved better overall health status/QoL in the middle ($p<0.001$) and in the end of treatment ($p<0.001$), in addition to less adverse events related to the systemic treatment in the midpoint ($p<0.001$) and in the end ($p<0.001$). Still, the capecitabine group had a better functional scale ($p\leq0.002$) and social scale ($p<0.001$), in addition to less fatigue ($p<0.001$), less nausea and vomiting ($p<0.001$), less constipation ($p\leq0.004$) and better appetite ($p=0.005$) than the patients treated with standard chemotherapy in the middle of the treatment and/or in the end of the treatment.
Leinert et al.[23]	In patients in the age-range of 65-70 years, the global health status/QoL was at a lower level at baseline: 56.7 (CI 95%: 52.5-60.9) versus 60.1 (CI 95%: 58.9-61.7) compared to younger patients. There was an increase in nausea and vomiting, which occurred between the 1st and 3rd follow-up. After the 4th and 5th cycles, there was more difference between the groups, with more nausea and vomiting in patients <65 years: 23.5 (CI 95%: 21.3-25.7) versus 18.6 (CI 95%: 14.2-23.0) in patients of 65 to 70 years old. After the end of chemotherapy, the values decreased below the baseline in patients aged <65 years, but in patients aged between 65-70 years, remained above the baseline level. Side effects of systemic therapy increased during the chemotherapy and reached the higher levels in the 2nd follow-up, to patients aged <65 years: 45.4 (CI 95%: 43.7-47) and in the 3rd evaluation in patients with age between 65 and 70 years: 51.1 (CI 95%: 46.7-55).
Montazeri et al.[24]	Physical functioning improved over time ($p=0.001$), while there was a deterioration in functional scales: emotional ($p=0.001$) and cognitive ($p=0.001$). Global QoL scores show a floating status: (beginning 59.2±31.8, T3 71.3±25.6 T18 32.0±30.2, $p=0.001$). All symptoms increased after 3 months of follow-up (nausea and vomiting, loss of appetite, side effects of the systemic therapy with $p<0.001$ and diarrhea $p=0.003$) or after 18 months (fatigue, pain, dyspnea, sleep difficulties, arm symptoms: $p<0.001$ and upset by hair loss scale: $p=0.003$). Body image worsened over time ($p<0.001$), as well as sexual functioning ($p<0.001$) and the sexual enjoyment ($p<0.001$). The future expectative increased over time ($p<0.001$).
Perroud et al.[27]	There was no difference between the start of the treatment and the midpoint of chemotherapy treatment. Increase in emotional well-being ($p=0.045$) and additional concerns between the midpoint and the end of chemotherapy ($p=0.019$).
Sanford et al.[31]	Lower scores of HRQoL during treatment compared to before and after treatment ($p<0.001$). Participants with poor sleep quality reported worse global HRQoL, fatigue and depression. Of the four subscales of HRQoL, physical function (subscales of well-being: $p<0.001$) and functional ($p<0.001$) were associated with overall scores of sleep quality over time.
Shiroiwa et al.[28]	The results indicated that the utility scores in the DTX group were lower than in other groups. The utility scores in the ACP group ($p=0.0048$) and ACT group ($p=0.0001$) were higher.
Tachi et al.[35]	The scales of activity ($p=0.003$), physical condition ($p<0.001$) and psychological ($p=0.032$) of HRQoL decreased after chemotherapy and the score of social relations increased ($p<0.001$).

to be continued

Table 2. continuation

Author and reference	Results
Winters et al.[25]	Only the scales of functioning and pain worsened with breast reconstruction by autologous implant of tissue of the dorsal muscle (p=0.002 for both). HRQoL worsened from baseline until 3 months and improved between 3 to 12 months (p<0.010). Chemotherapy impaired global health/QoL (p<0.001), social functioning (p=0.001), fatigue (p=0.006), functional well-being (p<0.001) and total score of HRQoL (p <0.001). Early complications had adverse effects on global QoL (p<0.001), role function (p<0.001), social (p=0.001), fatigue (p<0.001), pain (p=0.001) and breast symptoms (p<0.001), as well as in the total score (p=0.0011), physical well-being (p=0.0011) and functional well-being (p<0.001). Long-term complications resulted in less impact, with an adverse effect only on body image (p<0.001). There was improvement after 3 to 12 months in global QoL, and social functioning, fatigue, pain (p<0.001 for all), breast symptoms (p=0.009) and depression (p=0.002), in addition to physical well-being and total score (p<0.001 for all).
Zhang et al.[29]	The HRQoL components oscillated during the follow-up, ending with lower scores than baseline: physical well-being (p<0.001), social well-being (p<0.001), emotional well-being (p<0.001), functional well-being (p<0.001) and additional concerns (p<0.001).

Captions: ACP: Anthracycline followed by paclitaxel; ACT: Doxorubicin and cyclophosphamide followed by docetaxel; ACTH: Doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab; AE: Adverse events; AT: Doxorubicin and docetaxel; DI-EC: Adjuvant epirubicin in dense dose and cyclophosphamide administered with filgrastim and progenitor cellular support; DTX: Docetaxel; EC-T: Epirubicin, cyclophosphamide and docetaxel; EC-TH: Epirubicin, cyclophosphamide, docetaxel and trastuzumab; FAC: Fluorouracil, doxorubicin and cyclophosphamide; FEC: Fluorouracil, epirubicin, cyclophosphamide; FEC-D: Fluorouracil, epirubicin, cyclophosphamide followed by docetaxel; FEC-DG: Fluorouracil, epirubicin, cyclophosphamide followed by docetaxel and gemcitabine; HRQoL: Health related quality of life; PTX: Paclitaxel; QoL: Quality of life; SD-CT: Anthracycline-based chemotherapy; TAC: Docetaxel, Doxorubicin and cyclophosphamide; TCH: Docetaxel plus carboplatin.

worsening the HRQoL of women with breast cancer. Thus, it was observed that all the chemotherapy protocols affect one or more than one scale. In short, global health decreases during chemotherapy, but it can improve after treatment ends. The increase in symptoms is well reported and impaired the patients' HRQoL. However, most symptoms subside after the end of chemotherapy. The scales of body image, sexual function and physical functioning worsen throughout the treatment. Mental/psychological QoL has oscillations during the treatment as well as the scale about social support. In addition, chemotherapy caused adverse events that, despite being transient, impacted the physical condition of the patients. Thus, and considering that the results reported by the patients about HRQoL (such as physical, emotional functioning and treatment-related side effects) are increasingly most important, it appears that the changes caused during chemotherapy generate changes in the routine of the patients, a fact that changes the perceptions about HRQoL.

One of the factors that can negatively impact the HRQoL of the patients is the emotional issue, triggered after the start of treatment. Similar result was found in an integrative literature review[38] that reports that patients have little psychosocial support, causing a low score in the psychological domain of HRQoL. In addition, in a study[31] that assessed depression and anxiety scores, the levels of these scores worsen during chemotherapy, being associated with low levels of HRQoL. Therefore, it can be inferred that the low score on cognitive/emotional function may be associated with the effects of treatment, but it can also evolve due to prolonged emotional suffering.

There are questions about the way the patient relates to other people in her social relationship which can impact the HRQoL. Although perceptions about social relationships are not fully understood, this scale seems to be related to the way the patient faces the stages of treatment and to the social support provided by her family and friends. This fact agrees with the results of another review of the literature[39]. According to this study, the way how the patient perceives the familiar context is changed according to the level of social receptivity of the family[39]. In this context, there are no changes in HRQoL if the patient has familiar bonds with low social receptivity, but, if it has a high level of social receptivity, there is an improvement in HRQoL (due to the possibility to express their feelings, uncertainties and the need for family support).

The present study has as limitation the difficulty in comparing the results of outcomes between studies, which used different instruments. It is emphasized that there is no global consensus about how the analysis of HRQoL must be measured, diversifying the way it is performed by each author. And that, even though the questionnaires are specific for analysis of HRQoL, different terminologies are utilized in the nomenclature of the scales, in addition to the differences between questions used in each questionnaire to calculate the final score of the modules. Even so, the most used instruments to evaluate the

HRQoL in the studies analyzed by this integrative review were like to those found in another review[40].

Based on the results of this study, it is perceived that, in relation to the oncological care provided by the health professionals to patients, it became essential to develop a care plan comprehensive approach that identifies emotional, social and self-image changes, in addition to physical and functional. Still, it is suggested that issues related to the disease, such as side effects of the treatment, symptoms and sexual functioning should receive more attention, when considering the HRQoL of breast cancer patients. Further, this assistance should be extended to family members and spouses of patients, the approach of educational themes, in order to minimize the impact of treatment on social and sexual functions. This restructuring of the care provided requires the formation of multi-professional teams, which can assist the patient in all aspects related to HRQoL, including the patient and her perceptions of health in a global way.

CONCLUSION

From this review, it is concluded that the HRQoL of women with breast cancer is negatively affected by chemotherapy. It is noticed that the symptom scales showed the biggest changes when comparing the beginning with the end of the treatment. Thus, data on the assessment of HRQoL provide evidences that some clinical decisions must consider the patient's perception of their own health.

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There is no conflict of interests to declare.

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