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REVIEW ARTICLE

Prevalence and burden of oral complications in breast cancer: systematic literature review

Evelyn Gómez-Espinosa[1] and Gabriela Marroquín-Velásquez[2]*

[1]Independent Researcher, London, UK; [2]Center for Research in Atomic, Nuclear and Molecular Sciences (CICANUM), Universidad de Costa Rica, San José, Costa Rica

Abstract

Clinical management of breast cancer (BC) survivorship rarely involves evidence-based oral care. This review aimed to provide data on the prevalence and burden of oral complications (OC) among BC patients and to provide recommendations for optimal management of OCs in this population. The review was conducted using systematic searches in electronic databases up to July 2023 following a predefined protocol (CRD42021272130). The occurrence of at least one OC, beyond the well-known mucositis or stomatitis, was reported by 14% of close to 8,000 BC patients with an average age of 54 years. The most prevalent were periodontitis, gingivitis, ulcers, pain, tooth loss, or xerostomia. When evaluated, OCs were more prevalent in BC patients compared to controls and were mostly reported temporarily during treatment. A higher prevalence was observed from real-world data compared to interventional data. Although scarce and heterogeneous, burden data suggested that OCs negatively impact patients' quality of life and overall costs of treatment. OCs are scarcely studied but their occurrence impacts negatively patient's everyday lives. Standardized well-designed oral health research focusing on region-specific cost-effective management approaches is crucial for optimizing care delivery for BC survivors.

Keywords: *Oral health. Breast neoplasm. Adverse events. Epidemiology. Quality of life. Economics.*

Prevalencia y carga de complicaciones orales en cáncer de mama: revisión sistemática de la literatura

Resumen

El cuidado oral de supervivientes de cáncer de mama (CM) es un tema poco considerado en la práctica clínica. El objetivo de esta revisión es obtener evidencia médica sobre la prevalencia de las complicaciones orales (CO) y la carga humana y económica que estas generan en pacientes y sistemas de salud, además de presentar recomendaciones para el óptimo manejo de las CO en esta población. La revisión se realizó usando búsquedas sistemáticas en bases de datos electrónicas hasta julio de 2023, siguiendo un protocolo predefinido (CRD42021272130). La ocurrencia de al menos una CO, además de las comúnmente conocidas mucositis y estomatitis, se reportó por el 14% de cerca de 8,000 pacientes de CM con una edad media de 54 años. Las más prevalentes fueron periodontitis, gingivitis, úlceras, dolor, pérdida dental o xerostomía. Esta prevalencia se identificó más comúnmente en estudios de la vida real que en ensayos clínicos. La evidencia de carga humana y económica fue escasa y heterogénea, pero sugiere que las CO impactan negativamente en la calidad de vida y costos generales del tratamiento del CM. A pesar de que no son comúnmente estudiadas, las CO en pacientes con CM son numerosas e impactan negativamente en el tratamiento. La falta de investigación en salud oral estandarizada en la población oncológica representa un reto para el desarrollo de protocolos de atención oral personalizada de las sobrevivientes de CM.

Palabras clave: *Salud oral. Cáncer de mama. Eventos adversos. Epidemiología. Calidad de vida. Economía.*

***Correspondence:**
Evelyn Gómez-Espinosa
E-mail: evelynfporter@gmail.com

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Introduction

Breast cancer (BC) is the most prevalent neoplasm among women worldwide. According to the latest estimate from the World Health Organization (WHO), approximately 1.8 million women were living with the disease by the end of 2020, with an annual incidence of 58.5 new cases per 100,000 women[1]. Due to the extensive research, availability of early diagnosis, and effective treatment, most patients can expect a favorable prognosis with long-term BC survivorship care appearing to require region-specific multiple public healthcare interventions[2].

Unfortunately, the sequelae of pharmacological interventions include several adverse effects which can have long-lasting impact on patients, among them, oral complications (OCs). The most commonly OCs experienced by patients undergoing anticancer treatment in clinical trials are oral mucositis and stomatitis with a risk of serious events occurring in up to 46% of oncology patients[3]. In the case of BC specifically, our recent systematic review estimated that mucositis and stomatitis were reported accumulatively by 13 and 15%, respectively, among a cohort of 46,154 women with BC enrolled in 89 randomized controlled trials[4]. Our review also highlighted how all types of anticancer therapy increased the risk of developing mild-to-severe stomatitis or mucositis[5].

In addition to mucositis or stomatitis, recent systematic reviews have shown that cancer patients have a higher prevalence of less studied OC such as higher plaque index, gingival index, or post-extraction complications compared to healthy individuals ranging from 3 to 40%[6,7]. Unfortunately, these less studied OCs often go unnoticed or untreated in clinical practice due to lack of recognition or awareness[8]. To date, there has been no comprehensive review on their prevalence or their impact on the quality of life and economic burden for BC survivors. In addition, current aftercare guidelines for BC often overlook protocols for managing OC, which poses challenges for both research and clinical practice. This issue is particularly prominent in Latin American countries where dental procedures are often performed without considering the specific needs of special populations. In fact, dental treatment is often considered distinctly post-treatment away from their oncologic care.

By conducting an updated analysis on the epidemiology, burden, and treatment patterns of OC in BC survivors – with a focus on Latin American populations – we aim to provide a foundation for developing oral health management protocols tailored specifically for this group. In this article, we present more findings from our systematic literature review which includes the prevalence of less studied OC as well as the economic and humanistic burden associated with all types of OC experienced by BC patients undergoing pharmacological treatment.

Methods

Literature search

A systematic literature search was conducted following the registered protocol with the PROSPERO registration number CRD42021272130[5]. In brief, the systematic review followed the guidelines from the Cochrane Handbook[9] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[10] statement. Six electronic databases (Embase, Medline, Cochrane Database of Systematic Reviews, CENTRAL, Econlit, and LILACS) and complementary sources were searched for publications indexed up to July 2023. Key inclusion criteria included studies published in English or Spanish reporting on epidemiology, management, or burden of OC in adult women (≥ 18 years old) with any stage of BC who have received antineoplastic treatment. Search terms used to identify studies from databases are presented in supplementary table 1. The flow diagram depicting how the studies described here is presented in figure 1.

Descriptive analysis and quality assessment

Each included study was fully reviewed in duplicate. Main study and patient characteristics were tabulated alongside the outcomes of interest which included occurrence rate of OC or adverse effects.

The authors independently assessed the risk of bias and methodological quality of all included studies using best-practice instruments according to each study design.

Statistical method

Studies were categorized based on their design into observational and interventional data. The combined point prevalence of OC was estimated by the addition of the total number of BC patients reporting occurrence divided by the total sample size of all the studies reporting each OC.

Results

Prevalence of OC

At least one of eight OC including periodontitis, tooth loss, xerostomia, overall poor oral health, mouth ulcers,

Table 1. Prevalence of oral complications in breast cancer patients during treatment*

Oral complication (number of studies)	Sample size		All studies
	Real-world data	Interventional studies	Median prevalence [%] (range)
Periodontitis (n = 9)	267	116	55.0 (2.9-98.0)
Tooth loss (n = 7)	468	125	48.1 (23.0-100)
Xerostomia (n = 21)	1,997	3,357	44.8 (1.7-70.7)
Poor oral health (n = 7)	542	100	34.0 (21.9-95.1)
Mouth ulcers (n = 9)	583	862	26.1 (6.5-92.8)
Gingivitis (n = 12)	253	1383	25.0 (2.0-66.0)
Oral pain (n = 14)	422	3,833	17.3 (3.6-55.9)
Bleeding on probing (n = 4)	895	882	11.4 (3.2-50.0)

*The definitions, criteria, and the time related to treatment to capture the occurrence of OCs varied greatly in the included studies. The prevalence presented in the table refers to the occurrence of the complication of any grade or severity at any point from initiation to discontinuation of treatment.

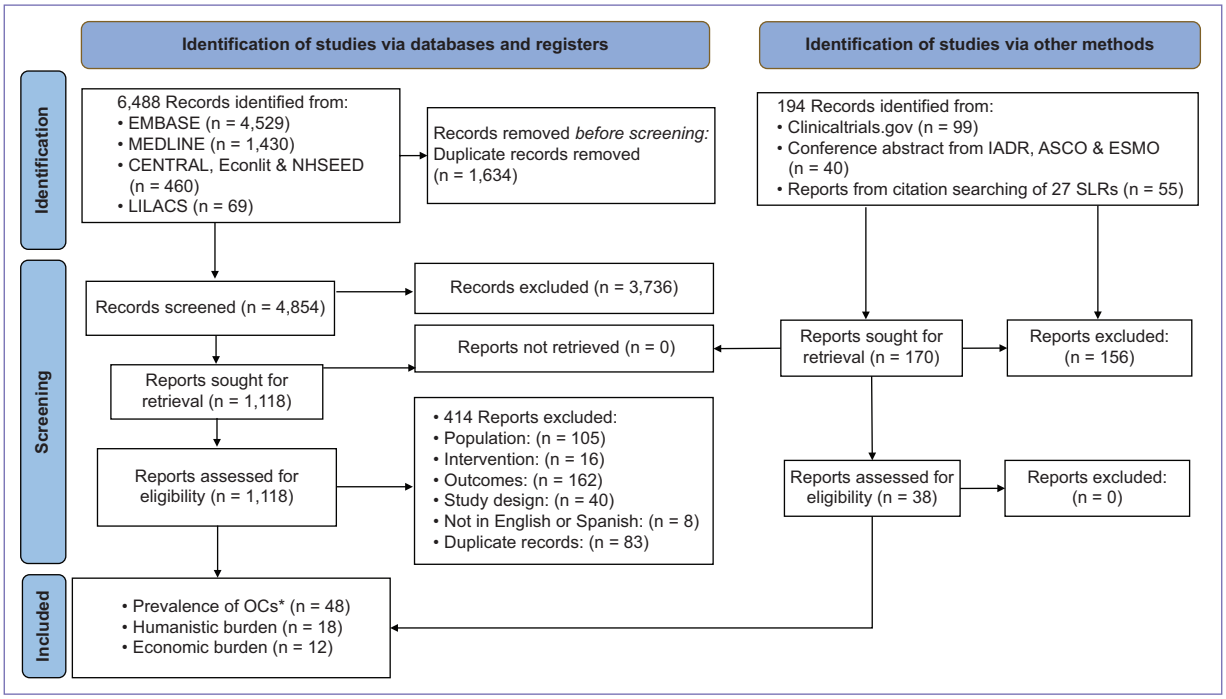
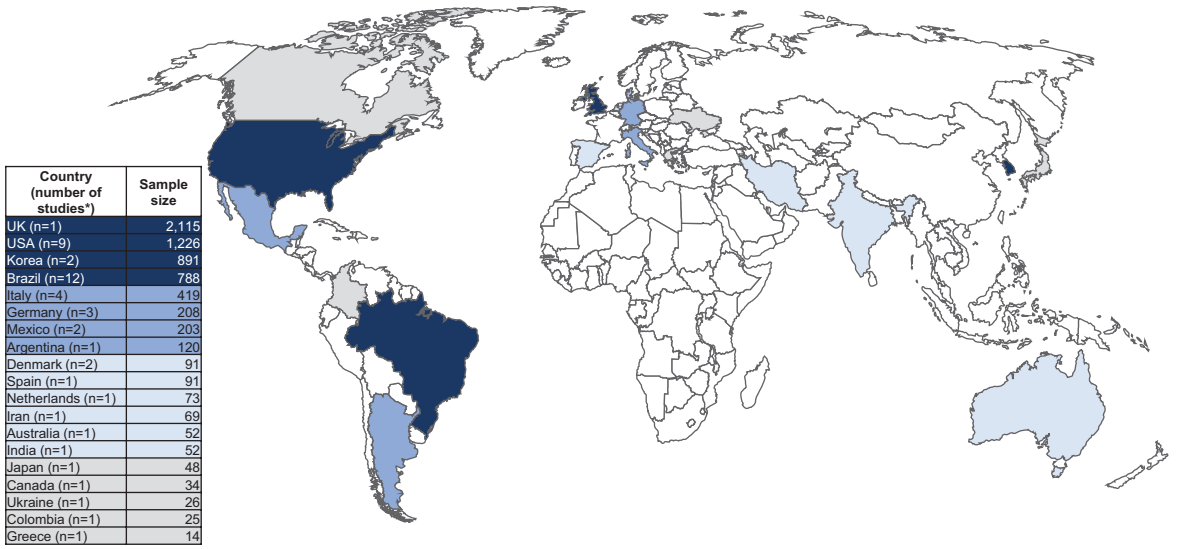


Figure 1. PRISMA flow chart summarizing the process of identification of the eligible and included studies summarized in this review. ASCO: American Society of Clinical Oncology; ESMO: European Society of Medical Oncology; IADR: International Association for Dental Research; LILACS: Literatura Latino-Americana e do Caribe em Ciências da Saúde; NHSEED: National health service economic evaluation database; OC: oral complications (*other than mucositis or stomatitis); SLR: systematic literature review.

gingivitis, oral pain, or bleeding on probing were prevalent in 7996 patients with an average age of 54 years old who received BC antineoplastic treatment based on data spanning from 1999 to 2022 from 48 studies carried out in 19 countries worldwide (Fig. 2). The study and patients' characteristics are outlined in supplementary tables 2 and 3. Most of the studies were observational of real-world data (n = 32) with moderate-to-high



Country (number of studies*)	Sample size
UK (n=1)	2,115
USA (n=9)	1,226
Korea (n=2)	891
Brazil (n=12)	788
Italy (n=4)	419
Germany (n=3)	208
Mexico (n=2)	203
Argentina (n=1)	120
Denmark (n=2)	91
Spain (n=1)	91
Netherlands (n=1)	73
Iran (n=1)	69
Australia (n=1)	52
India (n=1)	52
Japan (n=1)	48
Canada (n=1)	34
Ukraine (n=1)	26
Colombia (n=1)	25
Greece (n=1)	14

* Total number of studies does not add up to 48. There were two studies that were carried out in multiple countries (sample size:1,451) and were not included in this figure.

Figure 2. Geographic distribution of studies reporting on the prevalence of oral complications (OC) following breast cancer (BC) treatment. Darker shades indicate a bigger number of patients evaluated. The included studies reported the occurrence of at least one OC mostly from patients in Europe (n = 14) with data from 3037 patients, followed by North America (n = 12, 1,463 patients), East Asia (n = 3939 patients), and South America (n = 14,933 patients). *The total number of studies does not add up to 48 since there were two studies that were carried out in multiple countries (sample size: 1451) and were not included in this figure.

risk of bias primarily due to small sample sizes (under 100 patients, n = 22), a single-point data collection (cross-sectional studies, n = 14), or the self-reported OC occurrence (n = 14). Patients from observational studies predominantly had undefined BC stages (n = 23) or received undefined chemotherapy (n = 16). Conversely, the remaining studies evaluated BC interventions in highly selected patient groups (n = 16) with low-to-moderate risk of bias. Twelve studies used validated criteria or clinical expertise to identify OCs occurrence, and seven studies were randomized controlled trials. Most studies assessed the prevalence of OCs only once during (n = 30) or after (n = 7) BC treatment while nine studies captured OC occurrence before, during, and after treatment.

Table 1 presents the combined data of each OC's prevalence across all studies, and figure 3 shows the differences noted between observational and interventional studies. The median percentages for all eight OCs occurrence rates ranged from 11 to 55% with periodontitis figuring as the most frequently reported; however, the prevalence ranges were broad for all complications. Xerostomia was the most reported OC (n = 21) with close to half of BC patients (44%) recording its occurrence.

Real-world data indicated higher occurrences compared to interventional studies for six out of eight identified OCs (Table 1). For instance, real-world occurrence rate of periodontitis was threefold higher compared to interventional data. Conversely, oral pain and tooth loss exhibited similar occurrence rates across both study designs.

All the studies that compared OC prevalence to controls or overtime (n = 14) reported higher prevalence in BC patients that increased during treatment and decreased after treatment ceased. For instance, xerostomia was rarely reported before the initiation of chemotherapy but this symptom became a significantly prominent feature as treatment progressed, but this was reduced at follow-up. Furthermore, the likelihood of developing other OC increased with the occurrence of some OCs. For example, in adjusted analysis, BC patients had greater odds of developing melanotic macule, ulcers, or plaque when they have more than 13 missing teeth or xerostomia (2.39-fold (95% confidence interval [CI], 1.06-5.40) and 2.71-fold (95% CI, 1.14-6.42, respectively)[11].

Humanistic burden

There appears to be a lack of published studies specifically focused on BC treatment and their impact of

Table 2. Oral complications and QoL in breast cancer treatment assessed with oral-specific instruments

Author, year Study design Time of data collection Country	Population sample size Average age Cancer therapy	Oral complications/ oral adverse effects	Oral-health-related quality of life (OHRQoL) findings
Oral health-related quality of life (OHIP-14)			
Willershausen et al., 2019[12] Case-control NR 2004 - NR 2014 Germany	Early BC n = 80 Mean age: 60.5 years Chemotherapy	Median index for caries frequency (DMFT index): 19 (IQR 16–22)	Compared to control OR (95%CI) OHIP-German14: 3.14 (0.57; 17.19), p = 0.01 Depression score: 2.8 (0.9; 4.7) p = 0.0002-on average 0.5 points worse per missing tooth
Jardim et al., 2020[11] Cross-sectional Jan - Aug 2017 Brazil	BC (ICD-10, C50) n = 151 Mean age: 55 years Chemotherapy (not specified), radiotherapy and tamoxifen	Dental pain in the previous 12 months: 17.3% Xerostomia: 56.3% Lost at least one tooth: 87.4% Poor oral perception: 21.9%	OHIP-14 scores with a negative impact on QoL Functional limitation: 17.9% Physical pain: 18.5% Psychological discomfort: 26.5% Physical disability: 13.2% Psychological disability: 27.8% Social disability: 39.1% Social handicap: 20.5% Total score: 58.9%
Taichman et al., 2016[13] Prospective, longitudinal Apr 2009 - Sep 2010 USA	HR+BC n = 29 Mean age: 59.3 years Aromatase inhibitors (AI)	Xerostomia and periodontal disease Gum disease (swollen gums, receding gums, infected gums, or loose teeth): 38% Bleeding from your gums: 21% Gingival swelling: 13% Loose teeth: 17%	Mean OHIP-14 scores were poorest at baseline, improved at 6 and 12 months, and slightly worsened again at 18 months. OHRQoL scores at the four points in time showed a significant difference compared to controls (p = 0.005) Significant results (p < 0.05) compared to healthy controls Problems with teeth or mouth have cause more regular: Tension Worsened sense of taste Being self-conscious Difficulty relaxing Being irritable with other people Being embarrassed. Difficulty doing usual tasks.
Oral health-related quality of life (OHRQoL)			
Souza, 2022[14] Cross-sectional Oct 2019 - Aug 2021 Brazil	BC (not specified) n = 40 Mean: 56 years Aromatase inhibitors (AI)	Periodontitis Moderate/severe: 72.5%	OHRQoL mean scores compared to non-AI users Better OHRQoL (p = 0.005) Physical (p = 0.001) Social (p = 0.042) Psychological (p = 0.020)

BC: breast cancer; CI: confidence interval; DMFT: decayed, missing, and filled permanent teeth; HR+: hormonal receptor positive; IQR: interquartile range; OR: odds ratio; QoL: quality of life; NR: not reported; USA: United States of America.

their oral health complications. However, the evidence from 18 studies suggests that the occurrence of OCs negatively impacts the quality of life and everyday functionality of at least 7738 BC survivors who underwent treatment between 1999 and 2021. The studies were carried out around the world, mostly in the Americas (USA [n = 5] and Brazil [n = 4]) but also in Japan and UK (n = 2 each) and with one study each, Germany, Iran, the Netherlands, Saudi Arabia, and Spain. Most studies presented cross-sectional data (n = 10) of medium-to-low quality, while only three studies offered data from prospective cohorts and, despite OCs such as mucositis and stomatitis being a common occurrence in clinical trials, only two studies evaluated how these adverse events affected BC patients' quality of life. The outcomes reported are heterogenous, and the magnitude of different OC's impact in the quality of life of BC patients varies according to the type of instrument utilized, as follows:

Table 3. Oral complications and QoL in breast cancer treatment according to patients' perception questionnaires

Author, year Study design Time of data collection Country	Population Sample size Average age Cancer therapy	Relevant instrument (s)	Oral complications/ oral adverse effects	Oral-health-related quality of life (OHRQoL) findings
Alaqeel et al., 2019[16] Cross-sectional NR Saudi Arabia	Early BC (stages I to III) n = 59 Mean age: 48 years Chemotherapy (not specified)	Importance scores questionnaire of 12 pairs of hypothetical treatment side effects	Mucositis/stomatitis: 27%	Importance score for choosing treatment compared to other side effects: 2nd highest
Fall-Dickson et al., 2008[18] Cross-sectional NR USA	BC (not specified) n = 32 Mean age: 49 years Chemotherapy (not specified)	Oral Assessment Guide, the Oral Mucositis Index, the Painometer, the State-Trait Anxiety Inventory, the Beck Depression Inventory	Stomatitis and oral mucositis: 100%	Stomatitis-related Oral Pain: 47% Swallowing mean VAS score > 3 = 22% Sensory words chosen most frequently to describe the oral pain with swallowing Score: 86.7% Burning: 26.5% Aching or pressing: 26.7% Affective words chosen most frequently to describe oral pain with swallowing Annoying: 73.3% Nagging and miserable: 33.3% Troublesome: 26.7% Some degree of depression (mean = 10.2; SD=9.3; range=1-50): 100% Severity Minimal: 61% Mild: 29% State anxiety scores (mean = 34.2; SD=11.5; range of 20-60) Low: 64% Moderate: 32% High: 3%
Taichman et al., 2015[22] Cross-sectional Apr 2009-Sep 2010 USA	ER+BC n = 58 Mean: 61 years Aromatase inhibitors (AI)	Participant's self-perceived oral health, level of saliva and importance of dental health	Periodontitis Moderate/severe: 79%	How would you describe the health of your teeth (on a scale of 1 [poor/not important] to 5 [excellent/very])? 3.14 ± 1.18 p = 0.05 How would you describe the health of your gums? 2.97 ± 1.29 How important is your dental health? 4.72 ± 0.75 p = 0.09
Taichman et al., 2015[21] Cross-sectional NR 1999 - NR 2004 USA	BC (not specified) n = 177 Mean: 69.2 years Any	Perceived oral health	Gingivitis: 48.1% Periodontitis-moderate/severe: 20.1% Gingival bleeding: 4.1%	Perception of oral health compared to no BC Overall health (Fair/Poor): 28.9% p = 0.04 Limited foods due to teeth/mouth (often/sometimes): 13.9%
Taichman et al., 2018[15] Cross-sectional Jun 2014 - Jun 2015 USA	Early BC (stages I-III) n = 140 Mean age: 59.4 years Any	Perceived oral health	Xerostomia: 24% Mucositis: 2%	Oral concern-related responses: % Yes Problems with teeth or gums since diagnosis: 22% Do you believe your oral health problem is related to your cancer treatment? 27% Are you aware that cancer treatment may affect oral health? 68% Was there a time when you wanted to visit your dentist but could not due to your BC treatment? 25%

(Continues)

Table 3. Oral complications and QoL in breast cancer treatment according to patients' perception questionnaires *(continued)*

Author, year Study design Time of data collection Country	Population Sample size Average age Cancer therapy	Relevant instrument (s)	Oral complications/ oral adverse effects	Oral-health-related quality of life (OHRQoL) findings
Lo-Fo-Wong et al., 2016[19] Prospective cohort Mar 2011- Mar 2013 The Netherlands	BC (not specified) n = 746 Median age: 59 years Any	Psychosocial distress assessed with the validated Dutch version of the Distress Thermometer	Contact with a dentist to prevent or treat dental problems not specified	Odds ratio of having had contact with a dentist for patients with clinical distress 6 months post-diagnosis: 2.53 times higher (95%CI, 1.70-3.79) p < 0.05 15 months post-diagnosis: 1.98 times higher (95%CI, 1.322.98) p < 0.05
Nazari et al., 2021[20] Discrete choice experiment NR Iran	Metastatic HR+/ HER2- BC n = 78 Mean age: 51.4 years Hormonal and targeted treatments (1st line)	Relative attribute importance (RAI)	Stomatitis: NR	RAI: 12.3% (Rank 4 of 16 scenarios to rate the most important attribute of treatment)
Cameron et al., 2017[17] RCT Dec 2005 - Dec 2008 UK	BC (not specified) n = 1,238 Mean age: 59.2 years Epirubicin followed by Classical/Bonadonna CMF or oral capecitabine	Patient-reported toxicities questionnaire	Sore mouth: 58.3% Mouth ulcers: 43.3% Stomatitis (Stomatitis, Dry mouth, Oral candidiasis, Oral herpes): 67.0%	At the end of cycle 8 Distress caused by toxicity Sore mouth p < 0.0001 A little: 27.5% Quite a bit: 9.5% Very much: 6.8% Mouth ulcers p < 0.0001 A little: 17.9% Quite a bit: 5.6% Very much: 5.0% Daily interference caused by toxicity Sore mouth p < 0.0001 A little: 17.1% Quite a bit: 5.7% Very much: 4.8% Mouth ulcers p < 0.0001 A little: 13.1% Quite a bit: 3.9% Very much: 4.0%

BC: breast cancer; CI: confidence interval; CMF: cyclophosphamide methotrexate 5-fluorouracil; ER: estrogen receptor; HER2: Human epidermal growth factor receptor 2; HR: hormonal receptor; NR: not reported; QoL: quality of life; RCT: randomized controlled trial; SD: standard deviation; USA: United States of America; UK United Kingdom; VAS: visual analog scale.

Oral-specific instruments to measure quality of life

Of the 18 identified studies, only four[11-14] used one of two validated oral-specific instruments to assess quality of life: the Oral Health Impact Profile (OHIP-14) or the oral health-related quality of life (OHRQoL) questionnaire. Further details on their dimensions and scoring system can be found in supplementary table 4.

Table 2 summarizes the outcomes from studies that utilized OHIP-14 or OHRQoL. Overall, BC patients who received chemotherapy or aromatase inhibitors showed significant results indicating poorer oral and periodontal health along with higher numbers of missing or restored teeth compared to either a control group[12,13] or over-time[13]. These findings were associated with poorer physical and psychological well-being and a diminished oral-health-related quality of life. For instance, multivariate analysis of BC survivors' oral health data showed that they were significantly more likely of having a negative impact on OHRQoL compared to patients without them (Odds ratio: xerostomia 2.9 (95% CI 1.2-7.1); number of restored teeth: 1.9 (95%CI 1.0-3.9) p = 0.01 for both)[11].

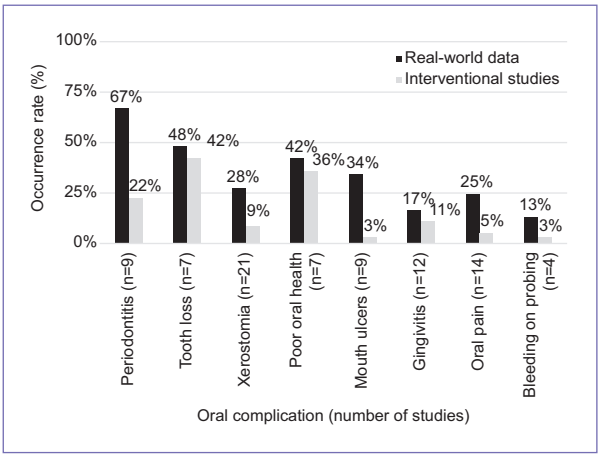


Figure 3. Prevalence of oral complications in breast cancer patients following treatment by study design.

Patient perception questionnaires and self-reported OHRQoL

Eight studies used different patient perception questionnaires to evaluate how the occurrence of OC impacts the quality of life of BC patients at all stages of the disease receiving various types of antineoplastic treatment[15-22]. Table 3 outlines the evidence gathered from patients concerning their BC treatment and the occurrence of OC. The evidence suggests that BC patients usually express lower self-perceived oral health compared to control groups. Oral pain, stomatitis, mucositis, and alterations in tasting or swallowing are highly scored among BC patients as bothersome or the source of distress and even depression. Conversely, other OCs such as dental problems were perceived as less detrimental to daily quality of life. For this population, receiving information from reliable sources and being involved in the choice of cancer therapy regime based on their preferences regarding different oral side effects would be crucial. However, this personalized approach is not common practice for most patients.

Generic instruments reporting OHRQoL

Six studies employed four generic instruments to assess the impact of OCs occurrence in BC patients with the EuroQoL-5D most commonly used (Table 4)[23-28]. These six studies measured the size effect on quality of life associated to mucositis, stomatitis, and oral pain at all severities (grades 1-4). The utility value (worse QoL) of these OCs decreased significantly after BC treatment in general. Results based on VAS scores suggested a bigger influence of oral adverse events on patients' QoL than those derived from EQ5D.

Economic burden

The evidence on the economic burden of OC associated with BC treatment was limited with only 12 studies were identified.

Seven of the 12 studies reported costs of managing stomatitis or mucositis (Table 5)[29-35]: four economic analyses of BC treatments and three retrospective cohort studies of moderate-to-high-quality data. The costs per stomatitis/mucositis episode of any severity were found to be approximately under $1,000 in BC patients in Spain[29] and the USA[35] during 2015 and 2016. However, for more serious events, requiring hospital care could cost escalate significantly to over $70,000[34].

Furthermore, six observational studies with very heterogenous outcomes reported moderate quality data on healthcare resource use due to different OC from BC (Table 5)[15,18,19,21,36,37]. Notably, chemotherapy was the most likely type of BC treatment that can significantly increase the use of dental care services and products to manage OCs compared to other treatments like aromatase inhibitors.

Discussion

This review follows the results of our recently published systematic literature review[5] and reports the prevalence of OC beyond the very well-studied mucositis and stomatitis. BC patients also experienced mostly xerostomia, periodontitis, gingivitis, or oral pain but also tooth loss, mouth ulcers or bleeding on probing, or poor oral health generally following treatment. The high occurrence of xerostomia and periodontitis was expected since they are common among the general population. This greater occurrence in BC survivors compared with controls may be associated with different factors. For example, we previously reported that older BC patients are at higher risk of developing mucositis, gingivitis, and poorer oral health overall[5] compared to controls without BC. In addition, patients' lifestyle behaviors such as alcohol consumption or smoking can increase the odds of developing OCs[38]. In the case of xerostomia, occurrence may be associated with a reduction in salivary flow stemming from hormonal changes the use of medications, exposure to antitumor treatments, and physiological or psychogenic causes, such as depression[39]. However, most data in this

Table 4. Oral complications and QoL in breast cancer treatment assessed with generic instruments

Author, year Study design Time of data collection Country	Population Sample size Average age Cancer therapy	Relevant instrument (s)	Oral complications/ oral adverse effects	Oral-health-related quality of life (OHRQoL) findings
Barbosa-Lima et al., 2020[24] Retrospective cohort Feb 2014-Feb2015 Brazil	BC (not specified) n = 196 Mean age: 59.2 years Chemotherapy (not specified)	CTCAE version 4	Mucositis (n = 97) Any grade: 49.5% Grade 1: 20.4 Grade 2: 23.0% Grade 3: 6.1% Grade 4: 0%	Symptoms following incidence of mucositis Fatigue: 94.8% (p = 0.01 compared with no mucositis) Pain: 41.8% Anxiety: 34.7% Depression: 26% Changes in self-image: 14.8% Changes in self-esteem: 10.2%
Marinho, 2020[26] Prospective cohort Mar 2017 - Feb 2019 Brazil	BC (not specified) n = 140 Mean age: 50.4 years Chemotherapy (Adriamycin, cyclophosphamide and paclitaxel)	EORTC QLQ-C30	Oral mucositis: 85.7%	Multiple linear regression model (β association) EORTC QLQ - C30 and oral mucositis Overall quality of life: –13.4 $p < 0.05$ Body image: –1.8 Perspective of future: –12.5 $p < 0.05$
Diernberger et al., 2022[25] Cross- sectional NR UK	BC (not specified) n = 4,135 Mean age: NR (> 18 years) Epirubicin followed by Classical/Bonadonna CMF or oral capecitabine	EQ-VAS and EuroQol-5D	Stomatitis (Stomatitis, Dry mouth, Oral candidiasis, Oral herpes): 53.2% Dysgeusia: 16.8% Mucosal inflammation: 45.3%	Decrease in quality of life connected to all grades of toxicity EQ5D Stomatitis: 0.0125 Dysgeusia: –0.0113 Mucosal inflammation: 0.0107 VAS: Stomatitis: 1.114 Dysgeusia: –0.892 Mucosal inflammation: –0.560
Prieto-Callejero et al., 2020[27] Cross-sectional May 2012 - Aug 2014 Spain	BC (not specified) n = 110 Mean age: 49.6 years Chemotherapy (docetaxel, epirubicin, and cyclophosphamide)	EuroQol-5D	Mucositis: 41.8%	Size effect on quality of life (Cohen d): 0.46 (significant when > 0.3) Patients with mucositis report having: Some problems performing my daily activities: 50.0% Moderate pain or discomfort: 63.0% A lot of pain or discomfort: 6.5% Moderate anxiety or depression: 28.9% Severe anxiety or depression: 11.1% Worse health status: 71.0%
Tachi et al., 2015[28] Cross-sectional Dec 2012 - Nov 2013 Japan	BC (not specified) n = 48 Mean: 59.6 years Chemotherapy (1st line)	EuroQoL-5D utility value, QOL-ACD	Oral mucositis (grade 1-3): 25% Oral pain (grade 1-3): 10.4%	After chemotherapy Oral mucositis EQ-5D utility value: –0.16 QoL-ACD %deteriorated Mobility: 33.3% Usual activities: 33.3% Pain/discomfort: 50% Anxiety/depression: 33.3% Oral pain EQ-5D utility value: –0.12 QoL-ACD %deteriorated Mobility: 20% Usual activities: 60% Pain/discomfort: 40% Anxiety/depression: 40%

(Continues)

Table 4. Oral complications and QoL in breast cancer treatment assessed with generic instruments *(continued)*

Author, year Study design Time of data collection Country	Population Sample size Average age Cancer therapy	Relevant instrument (s)	Oral complications/ oral adverse effects	Oral-health-related quality of life (OHRQoL) findings
Hagiwara et al., 2018[23] RCT NR Japan	Metastatic BC n = 380 Median age: 58 years Oral S-1 was compared with taxane (paclitaxel or docetaxel)	Health utility EuroQoL-5D-3L and the global health status in the EORTC QLQ-C30 at 3, 6, and 12 months	Oral mucositis Grade 1-2: 8.4% Grade 3-4: 0%	Oral mucositis impact on scores (95%CI) EORTC QLQ-C30 Grade 1 versus 0: –9.3 (–17.9, –0.6) p = 0.036 Grade 2 versus 0: –0.2 (–6.3, 6.0) p = 0.960 EQ-5D-3L based on societal preferences in Japan Grade 1 versus 0: –0.072 (–0.116, –0.028) p = 0.001 Grade 2 versus 0: –0.093 (–0.134, –0.053) p < 0.001 EQ-5D-3L based on societal preferences in the UK and the US. Grade 1 versus 0: UK: –0.083 (–0.148, –0.018) p = 0.012 USA: –0.067 (–0.111, –0.022) p = 0.004 Grade 2 versus 0 UK: –0.040 (–0.153, 0.074) p = 0.492 USA:–0.044 (–0.115, 0.028) p = 0.229 Disutility Grade 1: –9.3 (–18.3, –0.4) p = 0.04 Grade 2: –0.7 (–6.7, 5.4) p = 0.8

ACD: anticancer drug; BC: breast cancer; CTAE: common terminology criteria for adverse events; CI: confidence interval; CMF: cyclophosphamide methotrexate 5-fluorouracil; EORTC: European organization for research and treatment; QLQ: quality of life questionnaire; QoL: quality of life; NR: not reported; QoL: quality of life; RCT: randomized controlled trial; SD: standard deviation; USA: United States of America; UK United Kingdom; VAS: visual analog scale.

review were obtained cross-sectionally without controls making it challenging to associate them with BC treatment without longitudinal comparative research. It was also expected to find great variability in the occurrence rates of OCs between studies since there were noticeable differences in their methodology. Notably, most studies were observational and reported higher numbers of OCs compared to interventional studies. This finding might be explained by the observation of a similar systematic review of interventional studies which highlighted that most trials do not specifically address oral toxicities or include an oral clinical examination, which may lead to underreported and under-investigated oral toxicities[6]. Furthermore, when reported, most RCTs present only the occurrence of serious OCs (grades 3-4), and the prevalence of professionally reported OCs usually varies from self-reported OC. However, OCs can become serious or chronic overtime. Patients with "mild" OCs during treatment are not accounted for nor given adequate follow-up of their oral health leaving a gap in research and representing an unmet need for this population.

The humanistic and economic burden of OCs on BC patients undergoing treatment was also described. The evidence suggests that the occurrence of any OCs has a negative impact on BC patients with the number of events, the severity, and the exposure to chemotherapy associated with worse quality of life either perceived or measured and greater increased costs and resources use compared to those without OCs. These results align with similar studies across several types of cancer. For example, experiencing any chemotherapy-related AEs increased monthly healthcare costs with increasing costs associated to the greater number of

Table 5. Costs and health-care resource utilization associated with oral complications in breast cancer treatment

Author, year Study design Time of data collection Country	Population Treatment	Oral complications/oral adverse effects	Cost perspective Year/Currency Cost related to OCs
Frias et al., 2010[31] Cost-effectiveness model 2009 Spain	Metastatic BC Docetaxel versus Paclitaxel	Stomatitis grade 3/4 Docetaxel: 1.9% Paclitaxel: 0.2%	Societal perspective; 2009 EUR€ Costs of management per cycle: 475.49
Bermejo de Las Heras et al., 2018[29] Cost-of-illness model 2016 Spain	BC (not specified) Active treatment (any line) not specified	Stomatitis and mucositis (grade or prevalence NR)	Societal perspective 2016; EUR€ Costs of management per event: 968.0
Dranitsaris et al., 2015[30] Cost-utility analysis 2014 China	Metastatic BC Nab-paclitaxel, Docetaxel, or solvent-based paclitaxel	Stomatitis grade 3/4 Paclitaxel: 1% Docetaxel: 6.7% Nab-paclitaxel: < 1%	Societal perspective 2014; USD$ Cost of supportive care of symptoms and hydration per event: 5.0-5.65
Mittmann et al., 2010[33] Cost-effectiveness model 2006 Canada	Operable, axillary lymph node-positive BC TAC (Docetaxel+Doxorubicin and Cyclophosphamide) versus FAC (5FU, Doxorubicin and Cyclophosphamide)	Stomatitis grade 3/4 TAC: 2.6% FAC: 2.7%	Societal perspective 2006; CAD$ Costs of management in 6 months TAC: 3,151.18 FAC: 3,371.28
Rashid et al., 2016[34] Chart review Jan-Dec 2011 USA	Metastatic BC Capecitabine, Taxane, Cyclophosphamide, Doxorubicin, Gemcitabine, Epirubicin, Vinorelbine, Ixabepilone, or Eribulin.	Stomatitis (ICD code 528.0×) (grade or prevalence NR)	Payer's perspective 2013; USD$ Costs per episode of care (hospital care and treatment including mouthwashes, oral corticosteroids, mouth, and throat antiseptic, and topical oral anesthetics) - Single episode Outpatient: 5,096 Hospital: 27,781 -Multiple episodes ER+hospital: 71,708
Irwin et al., 2016[32] Retrospective cohort Jan 2006 - Dec 2013 USA	Metastatic BC (ICD-9-CM 174.xx) Biologic or chemotherapy	Mucositis/Stomatitis (ICD-9 CM 528.0×, 528.2, 478.11, 538, 616.81): 10.4% Incidence 17.2/100 person years	Payer's perspective, 2013 USD$ Costs per patient per month: 715.0
Wong et al., 2018[35] Retrospective cohort Jan 2006 - Sep 2015 USA	BC (ICD-9-CM 174.xx or 175.xx) Antineoplastic pharmacologic agent not specified	Stomatitis or mucositis Any grade: 0.8% (14% severe)	Payer's perspective 2015; USD$ Costs of management per episode: 961.0
Bozza et al., 2015[36] Retrospective cohort June 2013-Dec 2014 Italy	Early BC outpatients Adjuvant chemotherapy	Mucositis (grade or prevalence NR)	Healthcare resource utilization Unscheduled presentations to hospital: 8.5% (3rd most frequent reason among other adverse events)
Lo-Fo-Wong et al., 2016 Prospective cohort Mar 2011 -Mar 2013 The Netherlands	BC (any stage) Any treatment	At least one contact with a dentist: 31.9%	Healthcare resource utilization Factors associated with dental care use post-diagnosis OR (95% CI) Chemotherapy 6 months: 2.82 (1.76-4.50) highest most likely predictor 15 months: 1.93 (1.21-3.06) 2nd highest most likely predictor
Taichman, 2015 Retrospective cohort 1999-2004 USA	BC (any stage) Treatment NR	Odds ratio of developing moderate-to-severe event [OR (95% CI)] Gingivitis: 1.24 (0.64-2.53) Periodontitis: 1.7 (0.96-3.02)	Healthcare resource utilization Dental visit last 12 months: OR (95% CI) compared to more than 12 months ago Gingivitis: 0.74 (0.53-1.14) Periodontitis: 0.47 (0.44-0.68)

(Continues)

Table 5. Costs and health-care resource utilization associated with oral complications in breast cancer treatment *(continued)*

Author, year Study design Time of data collection Country	Population Treatment	Oral complications/oral adverse effects	Cost perspective Year/Currency Cost related to OCs
Taichman, 2018 Retrospective cohort Jun 2014 - Jun 2015 USA	BC (any stage) Chemotherapy, Tamoxifen, or aromatase inhibitors (AI)	Responses to the question in the past 3 months have you had (1 = "Never", 2 = "Hardly ever", 3 = "On occasion", 4 = "Fairly often" to 5 = "Very often.") Chemotherapy Mouth sores or mucositis: 2.14 ± 1.09 Mouth feels dry: 2.53 ± 1.42 Change in taste: 3.57 ± 1.67 Bleeding gums: 1.50 ± 1.00 Aching in mouth, teeth, or jaw: 1.50 ± 0.96 Tamoxifen Mouth sores or mucositis: 1.65 ± 1.18 Mouth feels dry: 2.31 ± 1.44 Change in taste: 1.84 ± 1.45 AI Mouth sores or mucositis: 1.36 ± 1.18 Mouth feels dry: 2.60 ± 1.48 Change in taste: 1.62 ± 1.20	Healthcare resource utilization Products requested from the dentist for treatment Mucositis Chemotherapy: 4% Tamoxifen: 0% AI: 0% Xerostomia Chemotherapy: 18% Tamoxifen: 20% AI: 29%
de Araujo Sensever, 2022 Cross-sectional study Jan 2007 - Aug 2007 Brazil	BC (any stage) Tamoxifen	Xerostomia: 70.7% Untreated dental caries: ≤ 1: 72.1% > 1: 27.9% Tooth loss: Mean ± SD 12.96 8.88	Healthcare resource utilization Use of dental services in a year is associated with missing more than 12 teeth: OR 3.29 (CI 95% 1.59–6.77)
Fall-Dickson , 2008 Cross-sectional NR USA	BC (not specified) n = 32 Mean age: 49 years Chemotherapy and autoHSCT	Oral pain: 47%	Healthcare resource utilization Topical anesthetics for oral pain Ulcerease: 9% used 2-6 times/day Viscous lidocaine: 6.3% 6 times/day Mouthwash (equal parts: Maalox, viscous lidocaine, nystatin suspension, benylin syrup): 6.3% 2-4 times/day

AI: aromatase inhibitors; BC: breast cancer; CI: confidence interval; NR: not reported; OR: odds ratio; USA: United States of America.

events and hospitalization rates among those experiencing more events[40]. A systematic review of the literature on the economic implications of preventing and managing OCs up to 2017 reported incremental costs of oral mucositis in the immediate term after cancer therapy at approximately $5,000–$30,000 US dollars among patients receiving radiation therapy and $3,700 per cycle among patients receiving chemotherapy with related hospitalizations or long-term medication as the major drivers of costs[41]. The economic impact of OCs could be significant for patients or healthcare systems. For example, this review described xerostomia with a prevalence up to 70% of BC patients and they would have required long-term sialagogues prescriptions at a cost of $40–$200 per month[41]. Important gaps in the knowledge of OCs associated productivity and out-of-pocket costs could further impact patients' economy for which large-scale micro-costing studies are required.

The main limitation of this review is the inability of providing a meta-analysis which is mostly due to the heterogeneity not only of the definitions of the population, their treatment, and the OC but also the instruments applied in their evaluation. In addition, most identified studies were of moderate-to-low quality due to single data-point collection, lack of controls, small

Table 6. Recommendations for future research and management of oral complications in breast cancer patients

Area	Recommendations
Clinical trials and medical research	Better definition and characterization of a broader range of oral complications that are constantly and consistently reported in a standardized way. Involvement of oral medicine specialists to improve the recognition and management of OCs. Multi-center, prospective population-based studies of the incidence, quality of life impact, and costs of OCs according to specific treatment agents are greatly needed to support evidence-based coverage and reimbursement policies.
Clinical practice	Preventive measures of good oral hygiene should be encouraged throughout including appropriate brushing and dental floss use techniques. Before BC treatment begins: – Provision of complete information about the spectrum of oral complications likely to develop during treatment, either acute or chronic oral effects. – Full dental clinical examination, including periodontal chart, and soft- and hard-tissue assessment (including X-rays) to identify and treat odontogenic pathologies to prevent exacerbation or incidence of OC. – Risk identification of gingivitis, and periodontal disease. – Tailored recommendations and treatment for identified oral diseases in hand with the oncology team advice. During BC treatment – Periodic dental assessment based on the risk identification of gingivitis and periodontitis. – Treatment for any identified oral complications provided in agreement with the oncology team. This may include dose reductions or discontinuation of treatment. After BC treatment – Periodic dental assessment and oral hygiene screening integrated in the comprehensive management of survivorship.

sample sizes, as well as bias from patients self-reporting of outcomes. It would be appropriate to further investigate the associations of incidence and severity of OCs overtime per type of treatment.

OCs may further lead to patient morbidity and negatively affect patients' physical and psychological well-being. Standardizing instruments for diagnosing and managing less well-studied OCs could enhance collaborations between dental and medical professionals as we gain better understanding of the linkage between oral and systemic health. Understanding the pathogenesis of OCs from BC therapy may lead to the development of biomarkers for predicting adverse events and new preventive or therapeutic strategies in the future to improve patient care outcomes.

Conclusions and recommendations

Based on the findings of this study, our previous publications, and expert clinical opinion, the recommendations for future research and for the oral evaluation and treatment of BC patients are presented in table 6. This review highlights an important gap of awareness and information of the oral health in BC but could apply to other solid tumor oncology patients.

Several OCs beyond the well-known mucositis or stomatitis are more commonly experienced by BC patients compared to controls including periodontitis, xerostomia, oral pain, taste alterations dental problems, and gingivitis. These negatively impact patients' everyday lives and also represent an economic burden.

By comprehensively understanding the epidemiology and burden of OC, health-care providers can proactively develop and implement survivorship care strategies to significantly enhance BC patient outcomes and quality of life.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

Supplementary data

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