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Epidemiology and burden of oral complications (OCs) following breast cancer treatment: A Systematic Literature Review - Risk factors for development of OCs

Epidemiología y carga de complicaciones orales (OCs) después del tratamiento del cáncer de mama: una revisión sistemática de la literatura: factores de riesgo para el desarrollo de OCs

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ABSTRACT: Breast cancer (BC), the most prevalent malignancy among women, has good survival rates given the numerous treatments available according to disease and patient characteristics. However, all treatments are associated with several adverse effects (AE) including oral-health complications (OC). Negative oral health is commonly reported during and after BC treatment, yet OCs are often overlooked or receive delayed interventions that are mostly performed empirically. This systematic literature review (SLR) aims to generate evidence that can provide the basis for the development of oral health management protocols for this particular population. **Methods:** Systematic searches on the epidemiology and burden of OCs after any BC treatment were conducted in seven electronic databases including Embase and Medline until July 2023. The authors screened all articles independently against pre-determined criteria and assessed for quality following the Cochrane Collaboration and PRISMA guidelines. Protocol registered in PROSPERO (CRD42021272130). Here, we describe the data on the risk factors for development of OCs. **Results:** Out of the 6,488 unique records identified, 1,118 full-text articles were assessed for eligibility and 742 articles met the inclusion criteria. The number of publications has increased overtime from 1979 to 2023, predominantly with interventional studies assessing the efficacy of treatment for BC (non-randomized interventions or randomized controlled trials, n = 549). The incidence of mucositis or stomatitis was reported in 85% of the all the included studies (n = 650). Most of the 48 studies assessing risk factors for development of OCs, evaluated the association of type of BC treatment. Overall, all chemotherapy regimens are reported to increase the risk of developing stomatitis and mucositis, but capecitabine users were significantly most likely to develop mild stomatitis and taxane-based therapies increased the risk of severe mucositis. The targeted therapy everolimus significantly increased the risk of developing severe stomatitis. Data in demographic risk factors to develop OCs is limited but there was an association reported between OCs and older age. **Conclusions**: This SLR shows that the incidence and impact of oral complications following BC treatment, other than mucositis and stomatitis, are underreported by the medical literature reflecting an unmet need for patients and an opportunity for research. The epidemiology, quality of life and economic burden of OCs, treatment efficacy and recommendations will be reported in future publications.

KEYWORDS: oral complications, breast cancer treatment, antineoplastic agent effects, adverse events incidence.

INTRODUCTION

Breast cancer is the most prevalent neoplasm among women worldwide. The World Health Organization (WHO) estimated that 1.8 million women were living with the disease by the end of 2020, and 58.5 new cases per 100,000 women are diagnosed every year (Sung *et al.*, 2021). Generally, due to the extensive research and availability of effective treatment, the majority of affected women can expect an excellent prognosis, with net 5-year survival rates of above 90% in the US (SEER, 2020), 88% in England (CRUK, 2021) and between 70-80% in Latin America (Sung *et al.*, 2021). Such differences may reflect inequity in access to treatment and systemic therapies according to healthcare systems but there are further regional distinctions described in breast cancer populations. For instance, while younger age

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is a predictor of survival in Hispanic breast cancer patients (Srur-Rivero and Cartin-Brenes, 2014), age has no association with survival in European populations (Escala-Garcia *et al.*, 2020). Thus, long-term breast cancer survivorship care appears to require region-specific public health interventions (L.S. Taichman *et al.*, 2013).

Treatment with neoplastic cytotoxic agents can affect a woman's oral health through damage of the sensitive soft tissues and bones of the oral cavity often causing acute to chronic dental or periodontal problems. In fact, cancer survivors have commonly reported serious oral health-related treatment side effects with up a third of those undergoing treatment estimated to develop oral complications (OC) (L.S. Taichman *et al.*, 2013). The most recent systematic reviews in the topic (up to 2016) reported that cancer patients had higher prevalence of dental complications including plaque index, gingival index or rate of post extraction complications with 3% to 40% compared to a healthy population (Hong *et al.*, 2018; Hong *et al.*, 2010). However, describing the epidemiology and burden of oral complications following breast cancer treatment has been confounded by a number of variables, including underreporting, differences in the terminology used to describe severity, differences in assessment techniques and scales, and the lack of associations between OC and other factors (Sonis, 2012; Sonis *et al.*, 2004).

Further, oral healthcare should be an im- portant component of cancer care and follow-up since oral conditions can significantly reduce the quality of life of patients, it can seriously affect functional capabilities to obtain appropriate nutri- tion, hydration, or overall comfort and, could pro- mote discontinuation or dose adjustment of treat- ment (Epstein *et al.*, 2012; Seiler *et al.*, 2014; S.T. Sonis *et al.*, 2004). However, in clinical practice, OCs often go unrecognized, underrated, untreat- ed and, the impact of cancer therapy on the oral health of these patients is rarely defined or eval-uated outside of mucositis associated with radio- therapy or chemotherapy (Peterson *et al.*, 2011). Current breast cancer care guidelines do not spe- cifically address OC protocols or are followed in research or clinical practice, specially, in LatinAmerican countries where empirical dentistry pro- cedures are often performed without distinction of special population's needs.

Therefore, the main objective of this systematic literature review (SLR) is to generate updated evidence in the epidemiology, burden and treatment patterns of oral complications in breast cancer survivors which can provide the basis for the development of oral health management protocols for patients with breast cancer who undergoing pharmacological treatment specially in Latin American populations. The review aimed to identify studies that address the following key research questions:

Epidemiology:

- What is the incidence of oral complications during or after treatment for breast cancer?
- What are the risks of developing oral complications during or after breast cancer treatment?

Burden:

- How does the presence of oral complications affect the quality of life of patients with breast cancer?
- What is the economic impact (costs and resource use) of managing oral complications in patients with breast cancer?

Management:

- Are there any guides/recommendations for managing oral complications in breast cancer patients during or after treatment?
- Are there any interventions that have been found effective in preventing or treating periodontal disease in patients with breast cancer?

METHODS

This SLR is registered with the International Prospective Register of Systematic Reviews (registration number CRD42021272130) and the full protocol is freely available on the PROSPERO website. The SLR methodology followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance (Page *et al.*, 2021).

DATA SOURCES

The electronic databases Embase, Medline, EconLit, NHS Economic Evaluation Database (NHSEED), Cochrane Database of Systematic Reviews (CDSR), CENTRAL and LILACS (Latin American and Caribbean Health Science Information were

searched for English or Spanish language publications indexed from inception to April 2022 (Gomez Espinosa and Marroquín Velásquez, 2022), with an update performed in July 2023. In addition, the proceedings from major conferences published since 2019 including the American Society of Clinical Oncology (ASCO) annual meetings, the European Society for Medical Oncology (ESMO), International Association for Dental Research (IADR), and the bibliographies of relevant systematic literature reviews were revised.

STUDY SELECTION

Studies were selected using protocol-defined eligibility criteria, detailed in supplementary Table I, following the Population, Intervention, Comparison, Outcomes and Study design (PICOS) framework. Briefly, the review included:

Population:

Adult women (≥18 years old) with any stage of breast cancer who have received antineoplastic treatment.

Intervention and Comparators:

Any pharmacological treatment or chemotherapy analyzed as single arm monotherapy or combination therapy, compared between them or against a control.

Outcomes:

- Incidence and risk factors of developing any oral complications.
- Humanistic burden (quality of life) and economic burden (costs, resource use) associated with oral complications.
- Recommendations or guidelines for management of oral complication in the population and intervention of interest.

Study design:

Interventional studies, observational studies, meta-analyzes.

Comprehensive searches were performed using the EMTREE, Mesh and database specific terms for breast cancer treatment and oral complications which included but were not limited to the following: periodontal disease, gingiva disease, stomatitis, mucositis and dental problems. Search strategies are presented in supplementary Table II.

Abstracts and full-text publications were independently screened by the authors against the inclusion criteria, with consensus achieved among them in case of discrepancies. Data were extracted by one researcher and validated by a second researcher. Relevant study and population characteristics and, outcomes data were extracted from the articles on predetermined tables by one author and fully validated by the other.

Risk of bias and quality assessment

The authors independently assessed risk of bias and methodological quality of all included studies using best-practice instruments according to each study design. Randomized controlled trials were assessed using the Cochrane Collaboration's tool, the quality of observational studies and economic models were assessed using risk the appropriate JBI's critical appraisal tool and meta-analyses studies were assessed using the AMSTAR2 tool.

RESULTS

Literature review

A total of 6,488 records were identified via electronic databases and 194 records were identified via other sources. After initial removal of duplicates, a total of 4,854 abstracts were screened and 1,118 were sought for retrieval and assessed for eligibility. A total of 413 studies did not meet the inclusion crite- ria and were excluded leaving 742 studies that fully met the inclusion criteria and were included in the review (Figure 1).

Overview of the entire body of evidence

A list of data availability and basic characteristics per study design for all included studies is presented in supplementary Table III. The number of publications reporting the epidemiology or burden of oral complications following breast cancer treat- ment has increased steadily overtime since 1979 (Figure 2A) with the highest number published in 2016 (n = 46). Overall, most identified studies were interventional compared to other study designs. Over half the 743 included studies were non-randomized interventional studies (n = 407), most of which were single-arm

Table 1. Treatments of breast cancer associated with incidence of stomatitis from meta-analyses data

Type of treatment	Reference	Number of included studies, data collection period, sample size	Treatment	Population	Stomatitis Grade 1-2	Stomatitis Grade 3-4
Chemotherapy	Nishijima, 2016	34RCTs, Up to Dec 2015, N = 4833	Capecitabine monotherapy dose 1,000 vs 1,250 mg/ m2 bid	Breast cancer patients	Random effects incidence (p value=0.437) 1,000 mg/m2 bid: 18.6 (95%CI 12.3-27.0) 1,250 mg/m2 bid: 15.3 (95%CI 11.5-20.1)	Random effects incidence (p value = 0.659) 1,000 mg/m2 bid: 1.9 (95%CI 1.1-3.2) 1,250 mg/m2 bid: 2.2 (95%CI 1.3-3.7)
	Yin, 2015	9RCTs, Jan 1998 - May 2015, N = 1798	Capecitabine-based chemotherapy	Advanced breast cancer (ABC)	–	RR:1.02 (95%CI 0.31–3.34) p = 0.976
	Huo, 2003	5RCTs, Up to Dec 2019, N = 3099	Capecitabine-based neoadjuvant and adjuvant chemotherapy	Early-stage triple-negative breast cancer	–	OR: 2.01 (95% CI 1.53-2.64) p < 0.001
	Zhang, 2016	5RCTs, 2001-2014, N = 1141	Chemotherapy regimens A = doxorubicin + paclitaxel; B = doxorubicin; C = capecitabine; D = CMF (cyclophosphamide + methotrexate + 5-fluorouraci); E = FAC (fluorouracil + doxorubicin + cyclophosphamide); F = doxorubicin + docetaxel; G = doxorubicin + cyclophosphamide; H = paclitaxel.	Metastatic/advanced breast cancer	OR (95%CI) All p > 0.05 CMF (cyclophosphamide + methotrexate + 5-fluorouracil)vs Doxorubicin + paclitaxel: 6.84 (0.17, 357.56) Doxorubicin: 3.43 (0.08, 172.19) Capecitabine: 13.11 (0.75, 428.91) FAC (fluorouracil + doxorubicin + cyclophosphamide): 10.95 (0.69, 233.50) Doxorubicin + docetaxel; G = doxorubicin + cyclophosphamide: 10.27 (0.15, 756.19)	–
	QI, 2012	3RCTs, Up to Oct 2011, N = 1109	Doublet vs single agent therapy (capecitabine, gemcitabine, ixabepilone or vinorelbine)	Metastatic breast cancer (MBC) patients pre-treated with an anthracycline and a taxane.	–	RR: 1.666 (95%CI 0.818-3.392), p = 0.160
	Yu, 2018	3RCTs, Up to Jul 2016, N = 844	Doublet vs. single-agent chemotherapy (CT) plus trastuzumab	HER2-positive metastatic breast cancer	–	RR: 5.02 (1.73 to 14.55) p = 0.003 NNTH = 25
	Li, 2009	2RCTs, 1974-2009, N = 1973	Ixabepilone plus capecitabine vs capecitacine monotherapy	Anthracycline- and/or taxane-resistant metastatic breast cancer	–	OR: 1.50 (95% CI 0.24–9.21) p = 0.66
	Zheng, 2015	8RCTs, Jan 1990 - Jan 2014, N = 2191	Taxane-based + anthracycline-based combination and anthracycline-based combination regimens	Advanced breast cancer (ABC)	Anthracyclines+ cyclophosphamide, HR: 1.57 1.07–2.31 0 0.006	Taxane-based + anthracycline-based combination regimens, HR: 1.44 (0.98–2.10) 0.063 Anthracycline-based combination regimens, HR: 1.49 (1.01–2.19) p = 0.312
Everolimus based	Raphael, 2018	7RCTs, NR, N = 2693	Everolimus (E) plus exemestane	Advanced hormone receptor positive breast cancer (BC) after progression on non-steroidal aromatase inhibitors	–	OR: 5.00, 95% CI 3.63-6.89
	Swarup, 2018	3RCTs, Up to Jan 2018, N = 1992	Everolimus (E)+ paclitaxel (P) + Herceptin (H) vs P+H, E+ exemestane (Ex) vs Ex, E+ vinorelbine (V)+ H vs V+H	Advanced breast cancer (ABC)	RR: 2.79 (95% CI: 1.77- 4.39) p < 0.001	RR: 9.58 (95% CI: 4.90-18.75) p < 0.001
	Wang, 2019	7RCTs, Up to Jul 2018, N = 1527	Everolimus plus endocrine therapy (fulvestrant or exemestane or letrozole or anastrozole or tamoxifen or toremifene) vs endocrine therapy alone	Hormone receptor-positive HER2-negative breast cancer	RR: 4.98 (95%CI 3.89,6.36) p < 0.00001	RR: 14.32 (95%CI 3.99, 51.47) p < 0.00001

Type of treatment	Reference	Number of included studies, data collection period, sample size	Treatment	Population	Stomatitis Grade 1-2	Stomatitis Grade 3-4
Everolimus based	Qiao, 2014	6RCTs, Up to Dec 2013, N = 3693	Everolimus plus exemestane vs placebo plus endocrine therapy.	Hormone receptor-positive metastatic breast cancer patients	RR: 5.44 (95%CI 4.63,6.38) p < 0.00001	RR: 9.28 (95%CI 4.77, 18.08) p < 0.00001
	Martel, 2018	4RCTs, Up to Jul 2017, N = 2063	mTOR inhibitors (everolimus, temsirolimus) in combination with (exemestane, fulvestrant,letrozole, tamoxifen)	Hormone receptor-positive metastatic breast cancer patients	–	OR 11.92; 95% CI 3.68–38.57 p < 0.05
Other targeted therapies	Xu, 2022	19RCTs, Jan 2020 - Nov 2021, N = 5608	PI3K/AKT/mTOR inhibitors	Hormone receptor-positive and HER2-negative metastatic breast cancer	Compared to everolimus Alpelisib: OR, 0.24; 95% CI, 0.035–1.0 Burparlisib: OR, 0.27; 95% CI, 0.052–0.96 Taselisib: OR, 0.32; 95% CI, 0.036–1.7 Pictilisib: OR, 0.80; 95% CI, 0.095–1.1	–
	Shields, 2020	11RCTs, Up to Aug 2019, N = 511	Alpelisib based therapy	Metastatic breast cancer (MBC)	AR: 0.28% (95% CI 0.23; 0.33) p = 0.45	AR: 0.01% (95% CI 0.0; 0.3) p = 0.04
	Zeng, 2016	6RCTs, Up to Jun 2015, N = 1387	Antiangiogenic kinase inhibitors (sorafenib, sunitinib, vandetanib, axitinib, motesanib)	Advanced breast cancer (ABC)	–	RR: 6.34 (2.88-13.98) p < 0.001
	Sultan, 2019	7RCTs, Up to Sep 2018, N = 4557	CDK4/6 inhibitors (palbociclib/ ribociclib/abemaciclib or placebo in combination with letrozole or anastrozole or fulvestrant or other hormonal agents)	Hormone receptor-positive HER2-negative breast cancer	RR: 2.160 (95% CI: 1.332-3.503) p = 0.002	RR: 2.097 (95% CI: 0.502- 0.753) p = 0.310
	Tun, 2017	5RCTs, Up to Jan 2017, N = 2021	CDK4/6 inhibitors (palbociclib-letrozole, palbociclib-fulvestrant, and ribociclib-letrozole vs placebo with letrozole or fulvestrant)	Hormone receptor-positive HER2-negative breast cancer	RR: 3.32 (95% CI: 2.09-5.28) p < 0000.1	RR: 2.01 (95% CI: 0.22-18.02) p = 0.53
	Abdel-Rahman, 2014	14RCTs, Jan 1966 - Jun 2014, N = 9813	Lapatinib-containing treatments vs control (no lapatinib)	Breast cancer patients	RR: 1.96 (95% CI: 1.07–2.67; p = 0.02	RR: 2.44 (95% CI: 1.41–4.22 p < 0.001)

Key: AR; accumulated risk; CI – confidence interval; HR – hazard ratio; NNTH – number needed to harm; OR – odd ratio; RCT – randomized controlled trial; RR – risk ratio.

Table 2. Treatments of breast cancer associated with incidence of mucositis from meta-analyses data.

Type of therapy	Reference	Number of included studies, data collection period, sample size	Treatment	Population	Mucositis Grade 1-2	Mucositis Grade 3-4
Chemotherapy	Sonis, 2004	96Trials, Jan 1966 - May 2002, N = 10530	Any chemotherapy	Breast cancer patients	–	R%: 8 (95% CI 8-9)
	Caparica, 2019	4RCTs, Up to Jun 2018, N = 4597	Anthracycline and taxane-based chemotherapy versus docetaxel and cyclophosphamide as adjuvant treatment	HER2-negative breast cancer	–	OR 2.57; 95% CI 1.81–3.64; p < 0.001
	Jones, 2006	17RCTs, 1999-2005, N = 2736	Chemotherapy or dose dense chemotherapy (A: adriamycin, C: cyclophosphamide, T: taxane [paclitaxel or docetaxel])	Early breast cancer (EBC)	–	Accumulated Risk % (95%CI) TAC: 4.92 (3.83, 6.07) A→T→C: 2.29 (1.30, 3.46) AC→T: 2.80 (1.40, 4.20) A→CT: 5.26 (2.63, 15.79) A→T:4.17 (1.67, 10.00) AT: 8.33 (1.39, 19.44) AC: 13.64 (2.27, 27.27) T: 2.87 (1.15, 6.90) All TAC regimens: 2.30 (2.24, 3.93)

Type of therapy	Reference	Number of included studies, data collection period, sample size	Treatment	Population	Mucositis Grade 1-2	Mucositis Grade 3-4
Chemotherapy	Lemos, 2012	4RCTs, Up to Dec 2011, N = 3418	Dose-dense (DD) regimens as adjuvant chemotherapy	Early breast cancer (EBC)	–	OR (95% CI): 3.07 (1.49-6.32) p = 0.002 NNH number needed to harm: 85
	Qi, 2013	4RCTs, 1980- 2012, N = 1122	Paclitaxel-based with docetaxel-based regimen	Metastatic breast cancer (MBC)	–	RR (95% CI): 0.082 (0.025-0.27) p < 0.001
Targeted therapy	Shields, 2020	11RCTs, Up to Aug 2019, N = 511	Alpelisib based therapy	Metastatic breast cancer (MBC)	AR: 0.18% (95% CI 0.14; 0.22) p = 0.36	–
	Zeng, 2016	6RCTs, Up to Jun 2015, N = 1387	Antiangiogenic kinase inhibitors (sorafenib, sunitinib, vandetanib, axitinib, motesanib)	Advanced breast cancer (ABC)	–	RR: 2.35 (1.19-4.63) p = 0.014
Combination	Wang, 2020	4RCTs, Jan 2000 - Oct 2019, N = 1842	Neoadjuvant Chemotherapy With or Without Bevacizumab	HER2-negative breast cancer	RR: 1.68 (95% CI 1.38-2.05) p< 0.00001	RR: 2.77 (95% CI 1.14-6.71) p = 0.02
	Yu, 2018	3RCTs, Up to Jul 2016, N = 844	Doublet vs. single-agent chemotherapy (CT) plus trastuzumab	HER2-positive metastatic breast cancer	–	RR: 0.49 (0.05 to 5.34) p = 0.559

Key: AR; accumulated risk; CI – confidence interval; NNTH – number needed to harm; OR – odd ratio; RCT – randomized controlled trial; RR – risk ratio.

Table 3. Characteristics of treatment for breast cancer associated with incidence of oral complications from observational studies.

Factor	Reference	Population (Sample size)	Treatment	Criteria/ instrument to measure OC	Mucositis	Stomatitis	
Treatment type	Komi, 2019	BC not specific (N = 166)	Anthracycline combination therapy (TAC, FEC, AC) with oral dexamethasone	–	OR: 3.28 (95%CI 1.32-8.19)	–	–
	Taichman, 2015b	Postmenopausal ER positive early BC (N = 58)	Aromatase Inhibitors (anastrozole, exemestane or letrozole)	Dental examinations and patient surveys	–	–	Risk % of Sites Bleeding on probing (BOP): 11.22 (1.63, 22.00) p = 0.02
	Souza, 2022	BC not specific (N = 40)	Aromatase Inhibitors (anastrozole, exemestane or letrozole)	Periodontal examination	–	–	Higher (worse) plaque index proportion (multivariate analysis) Aromatase inhibitors: users vs no users (p = 0.03)
	Bleachler, 2021	BC not specific (N = 2,445)	CDK4/6 inhibitor (palbociclib and fulvestrant)	ICD-9/10	–	Palbociclib-fulvestrant vs fulvestrant monotherapy HR: 5.0 (95%CI 1.1,23.1)	–
	Al Ibraheemi, 2016	Newly diagnosed BC (N = 75)	Chemotherapy (Adriamycin, Cyclophosphamide and Taxane)	WHO	Taxane included in protocols (p = 0.009)	–	–
	Tagawa, 2017	Early BC (N = 421)	Docetaxel	CTCAE version 4	Original vs generic All grade p = 0.142 Grade <3 p = 0.008	–	–
	de Lima, 2018	HER2-negative BC (N = 68)	Everolimus	–	–	OR: 2.29 p = 0.02 compared to other everolimus users (kidney or neuroendocrine cancer)	–
Treatment duration	de Araujo Sensever, 2022	BC not specific (N = 140)	Any	Decayed, Missing and Filled Teeth (DMFT) index	–	–	Tooth loss mean: Duration of tamoxifen (≤ 1 vs > 1 year) p = 0.030
	Acharya, 2017	Newly diagnosed BC (N = 52)	Adjuvant/neo-adjuvant chemotherapy (cyclophosphamide and adriamycin)	WHO	Mean grade (SD) Baseline:0 (0) 1st follow-up: 0.5 (1.1) p = 0.004 2nd follow-up: 0.5 (1.1) p = 0.001	–	Xerostomia compared to baseline 1st follow-up: p < 0.001 2nd follow-up: p < 0.001

Factor	Reference	Population (Sample size)	Treatment	Criteria/ instrument to measure OC	Mucositis	Stomatitis	
Treatment duration	Gong, 2017	HR+/HER2- advanced metastatic BC (N = 70)	Everolimus plus endocrine therapy	CTCAE version 4	–	Highest cumulative risk estimate: 42.9% after 2 weeks of treatment initiation	–
	Jardim, 2019	BC(ICD-10 code: C50) (N = 150)	Any	Patient interview and oral evaluation	–	–	OR (95% CI) p value Oral lesions >19 months since radiotherapy: 2.46 (1.13-5.34) 0.023 ≥ 30 months on tamoxifen: 2.23 (1.04-4.79) 0.038
	Lopez Pinto, 2020	BC not specific (N=27)	Neoadjuvant or outpatient adjuvant chemotherapy	Xerostomia Inventory, patients' surveys	–	–	Xerostomia Post-therapy: 1.74 [0.1: 30.66] p = 0.7
	Pedersini, 2022	Early BC (N=182)	Neo/adjuvant chemotherapy	CTCAE version 4	Increase occurrence from baseline p < 0.001 To 1st follow-up (2 months): +29% End on chemotherapy: +23%	–	–
Treatment dose	Bayraktar, 2020	BC not specific (N+719)	Neoadjuvant or adjuvant taxane-based chemotherapy	CTCAE version 4	–	Total dose of taxane received (lower dose higher occurrence): p = 0.0005 HR: 1.2 (95% CI 0.8-1.7) p = 0.02	–

Key: BC – breast cancer; CTCAE – common terminology criteria for adverse events; CI – confidence interval; HR – hazard ratio; OC – oral complication; OR – odds ratio; WHO – World health organization.

Table 4. Breast cancer patient characteristics associated with incidence of oral complications from observational studies

Factor	Reference	Population (Sample size)	Treatment	Criteria/ instrument to measure OC	Mucositis	Other OCs
Age	Karavasilis, 2016	Early BC (N = 453)	Anthracycline-containing adjuvant chemotherapy	WHO	≤65 vs >65: p-value <0.001	–
	Gadisa, 2020	BC not specific (N = 146)	Doxorubicin-cyclophosphamide (AC) and AC followed by Paclitaxel (AC-T)	CTCAE version 4	aOR = 1.04, (95% CI 1.003,1.068) p = 0.031 older age (>50 years)	–
	Musso, 2018	Early BC (N = 89)	Any	Dental examinations and patient surveys	–	>60 vs <60 years Gingivitis: OR 5,255; p = 0.029 Xerostomia: OR 3.460; p = 0.021
	Marinho, 2022	BC not specific (N = 140)	Any chemotherapy	Self-reported	–	Gingival bleeding (< 50 vs ≥ 50): OR: 0.28 [0.11, 0.73]
	Willershausen, 2019	Postmenopausal BC (N = 80)	Surgical therapy and additional radio- and chemotherapy	Number of teeth, caries frequency (DMFT), Sulcus Bleeding Index (SBI), the Approximal Plaque Index (API) and the Periodontal Screening Index (PSI)	–	Age association Number of missing teeth: 2.8% increase (95% CI 1.1%; 4.7%) per year of age (p = 0.0017). DMFT the median index for caries frequency (DMFT index): 0.9% per year, 95% CI (0.3%; 1.5%) p = 0.0038 Median number of root canal fillings: 2.2% per year, 95% CI (0.1%; 4.4%) p = 0.039 Average number of apical lesions: 1.02, 95% CI (0.99; 1.06) p = 0.1875 Sulcus Bleeding Index (SBI): (p = 0.0541)
	de Araujo Sensever, 2022	BC not specific (N = 140)	Any	Decayed, Missing and Filled Teeth (DMFT) index	–	Tooth loss mean: Age (≤ 65 vs > 65 years) p< 0.001

Factor	Reference	Population (Sample size)	Treatment	Criteria/ instrument to measure OC	Mucositis	Other OCs
Race/ ethnicity	Barbosa-Lima, 2020	BC not specific (N = 196)	Taxane-based (docetaxel, paclitaxel), anthracyclines (doxorubicin), adriamycin, cyclophsphamide) regimens	CTCAE version 4	White: OR 1.93 95%CI 1.04-3.57, p = 0.035 compared to black or mixed race	–
	Musso, 2018	Early BC (N = 89)	Any	Dental examinations and patient surveys	–	White vs black Xerostomia: OR 3.452; p = 0.047
	Taichman, 2015a	Postmenopausal BC (N = 164)	Any	NHANES dental health examinations	–	OR 95% CI compared to white Black Gingivitis: 1.13 0.66-1.72 Periodontitis (moderate and severe cases): 1.7 1.2-2.6 Hispanic & Mexican American Gingivitis: 1.52 0.92-2.43 Periodontitis (moderate and severe cases): 2.0 1.3-3.1
Other	Barbosa-Lima, 2020	BC not specific (N = 196)	Taxane-based (docetaxel, paclitaxel), anthracyclines (doxorubicin), adriamycin, cyclophsphamide) regimens	CTCAE version 4	Systemic metastasis: OR 5.46 95%CI 1.79-16.64, p = 0.002 compared to no metastasis or distal metastasis	–
	Amodio, 2014	BC not specific (N = 48)	Any	Oral examination	–	BC compared to healthy controls Median number of teeth: 0.03 % of sites with gingival bleeding: 0.04
	Souza, 2022	BC not specific (N = 40)	Aromatase Inhibitors (anastrozole, exemestane or letrozole)	Periodontal examination	–	Higher mean values of salivary inflammatory cytokines associated with the severity of periodontal disease (multivariate analysis) IL-6 (p = 0.004) IL-1 (p =0.002) IL-33 (p = 0.006)

Key: BC – breast cancer; CTCAE – common terminology criteria for adverse events; CI – confidence interval; OC – oral complication; OR – odds ratio; WHO – World health organization.

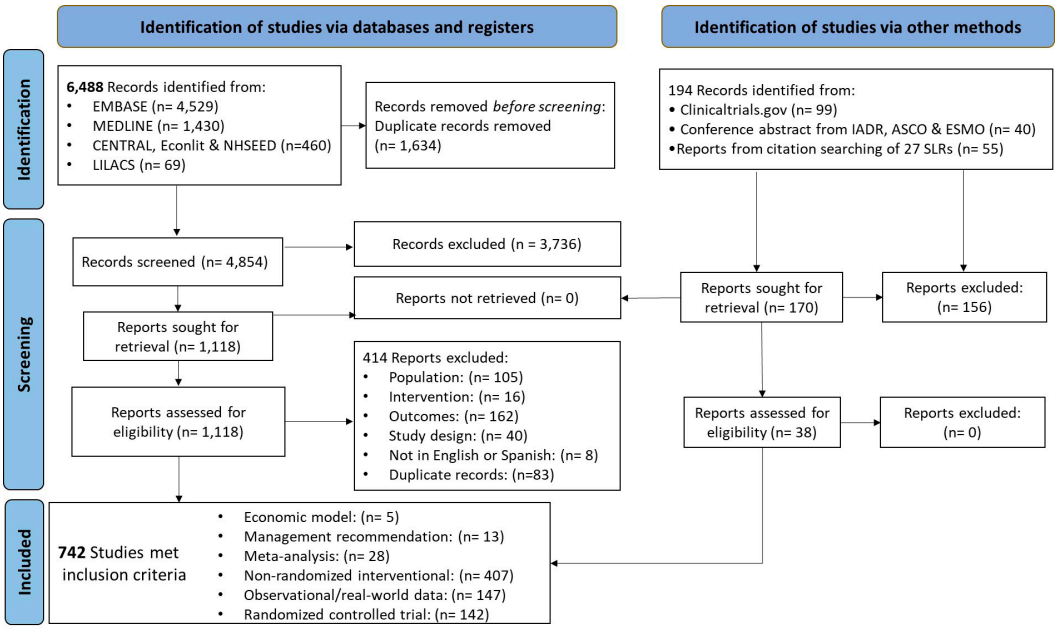

Figure 1. PRISMA flow chart summarizing the process for the identification of the eligible studies.

or uncontrolled studies assessing the effi- cacy of a treatment targeting breast cancer followed by similar number of observational studies reporting real-world data and randomized controlled trials of breast cancer treatments (n = 148 and n = 142 re- spectively), Figure 2B. Over 90% of the identified studies reported the incidence of oral complications following breast cancer treatment (686 of 742, Fig- ure 2C). The incidence of oral complications other than stomatitis or mucositis was only reported by 9% of these studies (Figure 2D).

Further, 48 attempted to identify the factors that might influence the incidence of oral complica- tions and 42 studies have explored the efficacy of therapies to treat oral complications. There were only 15 studies that offered recommendations to manage mucositis or stomatitis and, the burden that these complications inflict on patients, their families or healthcare systems was infrequently investigated with only 19 studies that reported on the impact on quality of life and 16 studies that reported on the im- pact on costs or resource use that oral complications inflict on patients. (Figure 2C).

Risk factors for development of oral complica- tions

Overview of studies

Of the 48 studies identified reporting the risk of developing oral complications following breast cancer (BC) treatment, 26 were meta-analyses of in- ternational randomized controlled trials data obtained via systematic reviews of studies published up until November 2021 which included large populations of BC patients of all stages of the disease (range 511- 10,530 patients). All the identified meta-analyses evaluated the risks of developing either mucositis or stomatitis associated to specific BC treatment. No other OCs were evaluated. Overall, the identified meta-analyses were of moderate to high quality ac- cording to AMSTAR2 criteria.

The remaining 22 publications were observational studies including 10 cross-sectional, 6 retrospective cohorts, 5 prospective cohorts and 1 case control study (Supplementary Table IV). The studies included patient data collected between 1999 and 2019, mostly from single oncology centers (n = 17).

The cohorts were geographically diverse but most studies were carried out in Brazil (n = 9), followedby the United States (n = 4), Japan (n = 2) and Chi- na, Ethiopia, Germany, India, Italy and Jordan (n = 1 each). Most analyses included less than 200 BC pa- tients (range 27-196 women) without specification of stage (n = 14), while 6 studies reported risk factorsin early or newly diagnosed BC patients. The oral complications mostly reported include mucositis, sto- matitis, xerostomia, and gingival problems. Fourteen studies reported the association between the type, frequency or duration of treatment and OC

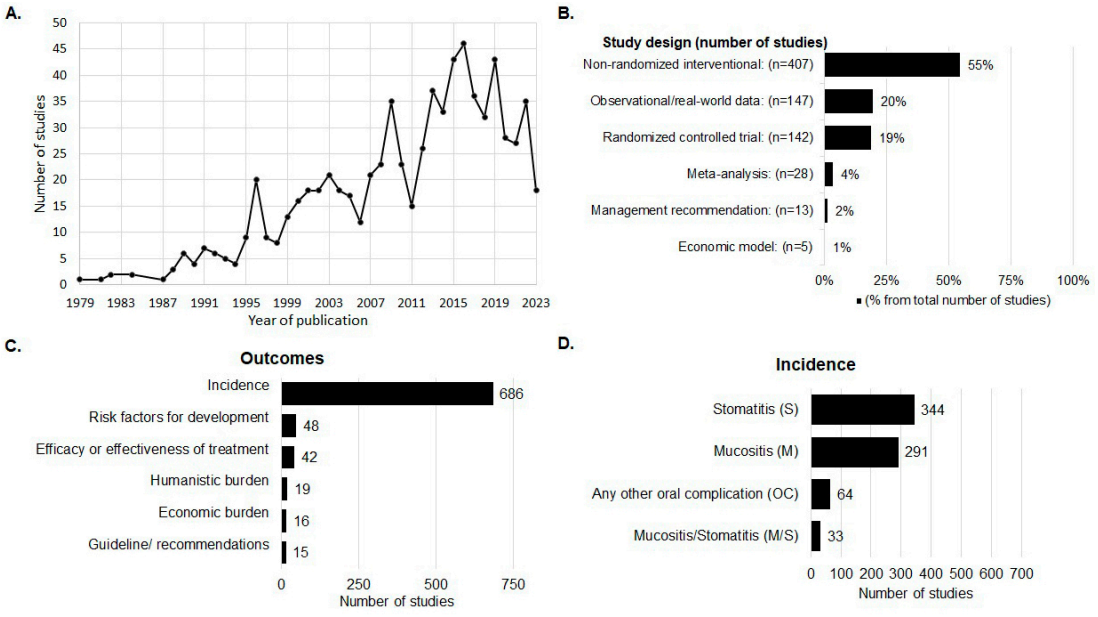

Figure 2. Distribution of characteristics of all studies that met the inclusion criteria and were included in the systematic literature review analyses.

incidence, while 10 studies explored demographic factors associated to the development of oral complications. These observational studies were of mostly medium risk of bias based on the JBI critical appraisal tools.

Risk of incidence of oral complications associated with treatment of BC treatment

Most of the included studies that explored the development of oral complications following BC treatment, either meta-analysis of clinical trials or real-world evidence, reported that the type or duration of treatment were the factors directly associated with their incidence (Tables 1-3).

The evidence identified of the impact of breast cancer treatment on the incidence of stomatitis is presented in Table 1 and Table 3. Eight meta-analyses of chemotherapies reported that all agents, either as monotherapy or in combination, increased the risk of developing mild stomatitis (grade 1-2), but patients treated with capecitabine were significantly most likely to develop mild stomatitis [Odds risk OR: 13.1; $p < 0.05$, (Zhang *et al.*, 2016)] and more severe stomatitis (grade 3-4) [OR: 2.01; $p < 0.001$, (Huo *et al.*, 2021)]. When targeted therapies were evaluated, the mTOR inhibitor everolimus was the most frequently reported as the type of treatment with the highest risk of stomatitis incidence as reported by 6 meta-analyses with significantly relative risks (RR) estimated between 2.79 (Swarup *et al.*, 2018) and 5.44 (Qiao *et al.*, 2014) for mild stomatitis and much higher risk for severe stomatitis [range RR = 5 (Raphael *et al.*, 2018) to 14.32 (Wang *et al.*, 2019)].

The risk of developing mucositis following BC treatment was evaluated in less studies (n = 14) compared to stomatitis (Table 2 and Table 3), but similarly, all chemotherapy agents studied increased the risk of severe mucositis. The highest risk was reported following the combination of adriamycin and cyclophosphamide at accumulated risk of 13.64 (Jones *et al.*, 2006). Further, the use of taxanes such as paclitaxel or docetaxel duplicated the risk of developing severe mucositis (Caparica *et al.*, 2019; Jones *et al.*, 2006).

Real-world data from observational studies (Table 3) supported the findings of the meta-analyses with chemotherapies increasing the risk of both mucositis and stomatitis and the use of everolimus to significantly increase the risk of stomatitis in breast cancer patients (de Lima *et al.*, 2018). Further, observational studies reported other oral complications incidence that are associated with BC treatment. For instance, aromatase inhibitors users had increased risk of bleeding (Taichman *et al.*, 2015b) on probing or worse plaque index (Souza, 2022).

In addition to the type of therapy, the duration of it was reported to increase the risk of developing OCs (Table 3). Interestingly, the data suggests that OCs occur early during therapy and the incidence remains long term.

Risk of incidence of oral complications associated with patients' characteristics

The relationship between the incidence of OCs in BC survivors and their characteristics was evaluated in 10 observational studies (Table 4). Older patients are at higher risk of mucositis (Gadisa *et al.*, 2020; Karavasilis *et al.*, 2016), gingivitis (Marinho *et al.*, 2022; Musso *et al.*, 2018), and poorer oral health overall (Willershausen *et al.*, 2019). In addition, white patients were reported to more likely develop mucositis (Barbosa-Lima *et al.*, 2020) and xerostomia (Musso *et al.*, 2018) compared to black patients, but less likely to develop gingivitis or periodontitis compared to black and Hispanic patients (Taichman *et al.*, 2015b).

DISCUSSION AND CONCLUSIONS

To the best of our knowledge, this is the most updated systematic literature review providing a comprehensive evaluation of the full spectrum ofthe epidemiology and burden of potentially doselim- iting oral complications in patients with breast cancer following treatment. Overall, this systematic literature review highlights the lack of recent research in the area of odontology as integral part of the careof breast cancer survivors reflecting an unmet need for patients and an opportunity for further research. Indeed, other studies have noted the lack of knowledge of about the potential oral effects of breast cancer therapies and about providing the best possible care for patients undergoing breast cancer treatment.

The review of risk analysis studies presented findings to support that treatment with chemotherapies increases the likelihood of developing mucositis and stomatitis with taxanebased therapies increasing

the risk of severe mucositis and capecitabine-based therapies significantly most likely to develop mild stomatitis while everolimus-based therapies signifi- cantly increase the risk of more severe grades of stomatitis. Certainly, most studies only reported the incidence of mucositis or stomatitis which could sug- gest that other oral complications are underreport- ed or not as prevalent as some data suggest. Yet, there is evidence from a survey of dental hygienists reporting that gingival inflammation, gingival bleed- ing, periodontal pocketing and xerostomia were the most common problems seen in BC survivors (Taich- man *et al.*, 2014). Oral complications reported such as xerostomia, bleeding on probing, gingivitis or periodontitis can be chronic conditions which require treatment and also affect patients' overall oral health and quality of life. Thus, the epidemiology and impact of other complications long-term requires awareness and recognition to promote research in prevention and appropriate management. Such interventions will require quality evidence to support the develop- ment of protocols for best patient care which is the ultimate aim of this review. Future publications using data from this systematic review will provide the de- scription of the results of the quality of life and economic burden associated with OCs in breast cancer, meta-analyses of the identified data to evaluate OC incidence and risk factors of development, as well as the published treatments efficacy and recommenda- tions for the management.

RESUMEN: El cáncer de mama (CM), la neoplasia maligna más prevalente entre las mujeres, tiene buenas tasas de supervivencia dados los numerosos tratamientos disponibles según la enfermedad y las características de los pacientes. Sin embargo, todos los tratamientos están asociados con varios efectos adversos (EA), incluidas complicaciones de salud bucal (OC). Comúnmente se informa sobre salud bucal negativa durante y después del tratamiento con BC, sin embargo, los AO a menudo se pasan por alto o reciben intervenciones tardías que en su mayoría se realizan de forma empírica. Esta revisión sistemática de la literatura (SLR) tiene como objetivo generar evidencia que pueda proporcionar la base para el desarrollo de protocolos de manejo de la salud bucal para esta población en particular. **Métodos:** Se realizaron búsquedas sistemáticas sobre la epidemiología y la carga de los AO después de cualquier tratamiento de BC en siete bases de datos electrónicas, incluidas Embase y Medline, hasta julio de 2023. Los autores examinaron todos los artículos de forma independiente según criterios predeterminados y evaluaron su calidad siguiendo la Colaboración Cochrane y PRISMA. pautas. Protocolo registrado en PROSPERO (CRD42021272130). Aquí describimos los datos sobre los factores de riesgo para el desarrollo de AO. **Resultados:** De los 6.488 registros únicos identificados, se evaluó la elegibilidad de 1.118 artículos de texto completo y 742 artículos cumplieron los criterios de inclusión. El número de publicaciones ha aumentado con el tiempo desde 1979 hasta 2023, predominantemente con estudios de intervención que evalúan la eficacia del tratamiento para el cáncer de mama (intervenciones no aleatorias o ensayos controlados aleatorios, n = 549). La incidencia de mucositis o estomatitis se informó en el 85% de todos los estudios incluidos (n = 650). La mayoría de los 48 estudios que evaluaron los factores de riesgo para el desarrollo de AO evaluaron la asociación del tipo de tratamiento de BC. En general, se ha informado que todos los regímenes de quimioterapia aumentan el riesgo de desarrollar estomatitis y mucositis, pero los usuarios de capecitabina tenían significativamente más probabilidades de desarrollar estomatitis leve y las terapias basadas en taxanos aumentaron el riesgo de mucositis grave. La terapia dirigida con everolimus aumentó significativamente el riesgo de desarrollar estomatitis grave. Los datos sobre los factores de riesgo demográficos para desarrollar AO son limitados, pero se informó una asociación entre los AO y la edad avanzada. **Conclusiones:** Este SLR muestra que la incidencia y el impacto de las complicaciones orales después del tratamiento con BC, distintas de la mucositis y la estomatitis, no están reportados en a literatura médica, lo que refleja una necesidad insatisfecha para los pacientes y una oportunidad para la investigación. En publicaciones futuras se informará sobre la epidemiología, la calidad de vida y la carga económica de los AO, la eficacia del tratamiento y las recomendaciones.

PALABRAS CLAVE: complicaciones orales, tratamiento del cáncer de mama, efectos de los agentes antineoplásicos, incidencia de eventos adversos.

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