

**ASSOCIATION BETWEEN ORAL MUCOSITIS AND XEROSTOMIA DURING BREAST CANCER CHEMOTHERAPY TREATMENT****ASOCIACIÓN ENTRE MUCOSITIS ORAL Y XEROSTOMÍA DURANTE EL TRATAMIENTO QUIMIOTERÁPICO DEL CÁNCER DE MAMA****ASSOCIAÇÃO ENTRE MUCOSITE ORAL E XEROSTOMIA DURANTE O TRATAMENTO QUIMIOTERÁPICO DO CÂNCER DE MAMA**

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**ABSTRACT**

**Introduction:** Chemotherapy can cause adverse events in the oral cavity, such as mucosal lesions and changes in salivary flow. However, the association between these events has not been evaluated. **Objective:** To evaluate the association between oral mucositis and xerostomia during chemotherapy for the treatment of breast cancer. **Methods:** This was an observational and prospective study carried out with 140 women who underwent chemotherapy treatment for breast cancer in three cancer centers, evaluating them in two segments: in the intermediate cycle and at the end of treatment. **Results:** A high frequency of oral mucositis (87.5%) and xerostomia (82.9%) was observed after exposure to chemotherapy agents, but there was no significant association between both in the study segments ( $p > 0.05$ ). However, 60% simultaneously manifested oral mucositis and xerostomia in at least one segment, with a significant association of the double-hit being observed between the studied segments ( $p < 0.001$ ). **Conclusion:** Oral mucositis and xerostomia were not consistently associated in breast cancer patients during chemotherapy. **Keywords:** Oral Health; Breast Neoplasms; Chemotherapy; Oral Mucositis; Xerostomia.

**RESUMEN**

**Introducción:** La quimioterapia puede ocasionar eventos adversos en la cavidad bucal, como lesiones mucosas y cambios en el flujo salival. Sin embargo, la asociación entre tales eventos no ha sido evaluada. **Objetivo:** Evaluar la asociación entre mucositis oral y xerostomía durante la quimioterapia para el tratamiento del cáncer de mama. **Métodos:** Se trata de un estudio observacional y prospectivo realizado con 140 mujeres que se sometieron a tratamiento quimioterápico por cáncer de mama en tres centros oncológicos, evaluándolas en dos segmentos: en el ciclo intermedio y al final del tratamiento. **Resultados:** Se observó una alta frecuencia de mucositis oral (87,5%) y xerostomía (82,9%) después de la exposición a agentes quimioterápicos, pero no hubo asociación significativa entre ambas en los segmentos de estudio ( $p > 0,05$ ). Sin embargo, el 60% manifestó simultáneamente mucositis oral y xerostomía en al menos un segmento, observándose una asociación significativa de la doble ocurrencia entre los segmentos estudiados ( $p < 0,001$ ). **Conclusión:** La mucositis oral y la xerostomía no se asociaron consistentemente en pacientes con cáncer de mama durante la quimioterapia. **Palabras claves:** Salud Bucal; Neoplasias de la Mama; Quimioterapia; Mucositis Oral; Xerostomía.

**RESUMO**

**Introdução:** A quimioterapia pode provocar eventos adversos na cavidade bucal, como lesões na mucosa e alterações no fluxo salivar. Entretanto, a associação entre tais eventos não foi avaliada. **Objetivo:** Avaliar a associação entre mucosite oral e xerostomia durante a quimioterapia para o tratamento do câncer de mama. **Métodos:** Trata-se de um estudo observacional e prospectivo realizado com 140 mulheres que realizaram tratamento quimioterápico para o câncer de mama em três centros oncológicos, avaliando-as em dois segmentos: no ciclo intermediário e ao fim do tratamento. **Resultados:** Observou-se uma alta frequência de mucosite oral (87,5%) e xerostomia (82,9%) após a exposição aos agentes quimioterápicos, mas não houve uma associação significativa entre ambos nos segmentos do estudo ( $p > 0,05$ ). Entretanto, 60% manifestaram simultaneamente mucosite oral e xerostomia em pelo menos um segmento, sendo observada uma associação significativa da dupla ocorrência entre os segmentos do estudado ( $p < 0,001$ ). **Conclusão:** Mucosite oral e xerostomia não estiveram consistentemente associadas em pacientes com câncer de mama durante a quimioterapia. **Palavras-chave:** Saúde Bucal; Câncer de Mama; Quimioterapia; Mucosite Oral; Xerostomia.



## INTRODUCTION

Breast cancer (BC) is common among women with cancer in Brazil, and more than 66.000 new cases are expected between 2020 and 2022. BC patients often manifest oral side effects (OSE) during chemotherapy (CT), such as oral mucositis (OM; mucosal lesion) and xerostomia (XT; dry mouth sensation), both due to the cytotoxic effect of antineoplastic agents<sup>(1,2)</sup>. The OM occurrence in BC patients varies, considering the design and sample sizing of each study. In a previous cross-sectional approach, between 2014 and 2015, the occurrence was approximately 50%<sup>(3)</sup>. However, there is no robust literature on the XT occurrence in BC patients<sup>(2)</sup>. To the best of our knowledge, this literature is even more sparse when considering longitudinal investigations.

From Brazil, there is a report of the simultaneous occurrence of OM and XT. However, this evidence comes from a cross-sectional and non-specific approach to BC<sup>(4)</sup>. Moreover, in head and neck cancer patients, there is evidence of an interaction between radiation-related OM and XT in other health-related outcomes<sup>(5)</sup>. The state of the art leads us to question whether there is an association between OM and XT in BC patients exposed only to CT. Then, the aim of this study was to describe the occurrence and association between OM and XT during CT to treat BC. The alternative hypothesis tested is ( $H_1$ ) there is an association between OM and XT in BC patients exposed to CT.

## METHODS

This was an observational and prospective report as part of a major study that was carried out in three cancer centers between March 2017 and February 2019 in Aracaju, Sergipe, Brazil. The main project received ethical approval (CAAE: 63009616.4.0000.5393), and each patient signed an Informed Consent Form. The follow-up segments were carried out in the intermediate cycle (IC) and at the end of chemotherapy (EC).

The population was women diagnosed with BC. The sample size was estimated at approximately 127 participants in the main study. BC patients who were not exposed to any cancer treatment previously (except other treatments for current BC, such as surgery) and who would be exposed to CT, without cognitive dysfunction or diabetes mellitus, were eligible. It is noteworthy that the treatment factor (CT) was prescribed by each cancer center and its professionals, without interference from this investigation, which only followed the treatment of each patient, studying a set of treatment-dependent outcomes.

BC patients were invited to participate as a convenience sampling. The evaluation was carried out before the CT session, in a private space at each service. Common Terminology Criteria for Adverse Events (CTCAE), version 4.03<sup>(6)</sup>, was used to assess OM, recorded as yes or no and

between grade 0 to 5 (assigning 0 for patients without OM). The XT was also recorded as yes or no, assessed by asking: do you usually feel your mouth dry?

To allow statistical analysis, *JAMOVI* software (v2.3.15; Sydney, Australia) was used. The significance level ( $p$ ) was set at 5% ( $\alpha = 0.05$ ). The OM and XT occurrence was described in absolute ( $N$ ) and relative (%) frequency. The OM severity was expressed as mean and median, following their dispersion measures (standard deviation and quartiles, respectively). The association was examined by McNemar's test (between IC and EC segments) and by Pearson's chi-square test ( $\chi^2$ ) (between OM and XT in each segment). Comparisons between OM scores splitted or not by XT (yes or no) were carried out using Mann-Whitney's test (in each segment) and Wilcoxon's rank test (IC versus EC segment), respectively. Also, the correlation was carried out using Spearman's correlation test (considering a non-normal distribution after the Shapiro-Wilk normality test).

## RESULTS

Table 1 shows the occurrence and association of OM and XT in women with BC exposed to CT, both in IC and EC segments. It is possible to observe, after the McNemar test, that there was a significant association between the XT and double-hit (concurrent OM and XT) among the segments of the study, indicating that manifesting them in the intermediate cycle may be related to manifesting them at the end of chemotherapy.

**Table 1** - Oral side effects (oral mucositis and xerostomia) occurrence and association between IC and EC segments in breast cancer patients exposed to chemotherapy.

Oral side effects	IC		EC		Overall		$p^{\ddagger}$
	N	%	N	%	N	%	
	<b>Oral mucositis</b>						0.898
Yes	90	64.3	89	63.6	120	85.7	
No	50	35.7	51	36.4	20	14.3	
	<b>Xerostomia</b>						0.003*
Yes	78	55.7	104	74.3	116	82.9	
No	62	44.3	36	25.7	24	17.1	
	<b>Oral mucositis + Xerostomia</b>						<.001*
Yes	39	27.9	67	47.9	84	60.0	
No	101	72.1	73	52.1	56	40.0	
$p^{\ddagger\ddagger}$	0.761		0.722				

$\ddagger$ : McNemar's test (IC versus EC segment).  $\ddagger\ddagger$ : Pearson chi-square test ( $\chi^2$ ; OM versus XT, both in IC and EC segments). \*: statistically significant p-value (<0.05).

In fact, most women experienced, either in IC or EC, the double-hit during CT treatment for BC. However, analyzing each segment individually, after Pearson's chi-square test, no association was observed between OM and XT, both in IC and EC segments. At last, it is observed that the frequency of OM was stable between the segments, while XT and double-hit (concurrent OM and XT) frequencies increased at the end of chemotherapy.

Table 2 shows OM severity in women with BC exposed to CT according to CTCAE criteria, both in IC and EC segments. It is possible to observe that most cases were mild and moderate, characterizing a low severity. In the IC and EC segments, considering the 90 and 89 OM cases, 94.4% and 97.7% were scored as 1 or 2 (mild or moderate), respectively.

**Table 2** - Oral mucositis severity in women with breast cancer exposed to chemotherapy according to CTCAE criteria.

Segment	Mean	SD	Median	Q1/Q3
<i>Intermediate cycle</i>	0.94	±0.88	1	0 / 1
<i>End of chemotherapy</i>	0.86	±0.78	1	0 / 1

SD: standard deviation. Q1/Q3: first and third quartile.

When correlating OM severity between IC and EC segments, there was no significant correlation after the Spearman's correlation test ( $p = 0.886$ ), as well as there was no difference in severity between the IC and EC segments after the Wilcoxon's rank test ( $p = 0.567$ ). When comparing the severity of OM between patients with and without XT, both in the IC and EC segments, no statistically significant difference was observed after the Mann-Whitney's test ( $p = 0.915$  and  $0.555$ , respectively).

## DISCUSSION

This investigation evaluated the occurrence and association between OM and XT in women with BC who were exposed to CT. It is necessary to consider that the increase in the double-hit in the EC segment is due to the increase in the XT occurrence observed later. On the other hand, the impact of XT on OM was certainly affected by the low severity of the latter, as a statistical issue.

Although a consistent association between OM and XT was not observed in this sample, the high frequency of both (including the double-hit) leads us to question how the simultaneous manifestation of OSE can affect the speech, chewing and swallowing functions of BC patients, in addition to the nutritional status and quality of life<sup>(1,4,5)</sup>. The impact of XT on oral-related quality of life of cancer patients, which often affects women, has already been described<sup>(7)</sup>. It is important to

consider that chemotherapy-induced XT can start in the first days of exposure and last until the end of treatment<sup>(8)</sup>, as demonstrated here. Nonetheless, as a limitation of the study, XT may be reported due to the use of medications (in addition to CT)<sup>(2)</sup>.

The occurrence of OM and XT (including double-hit) in our sample was higher than a previous study<sup>(4)</sup>. Then, it is important to note that OSE can be feared by cancer patients, in addition to raising health care costs<sup>(9,10)</sup>. Future investigations may clarify the impact of double-hit on cancer treatment experience and health-related quality of life, as well as which CT protocols may be related.

## CONCLUSION

The OM and XT occurrence was high in women with BC exposed to CT. However, no association was observed between them in the study segments, except for the double-hit. In addition, XT did not affect the OM severity.

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#### **Authorship criteria (author contributions)**

##### **Pablaine Matias Lordelo Marinho, Namie Okino Sawada:**

They substantially participated in the design, planning, collection and analysis of data, interpretation of results, writing and critical review of the final version

##### **Ricardo Barbosa-Lima, Glebson Moura Silva, Simone Yuriko Kameo:**

They substantially participated in the analysis and interpretation of data, writing and critical review of the final version. All authors approved the final submitted version.

#### **Declaration of conflict of interest**

Nothing to declare.