

Association between tamoxifen and tooth loss in women with breast cancer

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Abstract

Objectives

Investigate the effect of tamoxifen on the occurrence of tooth loss (TL) in breast cancer (BC) survivors.

Methods

A cross-sectional study was conducted with 140 BC survivors using tamoxifen therapy. Sociodemographic, medical and dental data were evaluated. TL was determined using the M component of the Decayed, Missing and Filled Teeth (DMFT) index. Logistic regression models were run to determine associations between the independent variables and outcome (TL).

Results

Mean TL was 12.96 (SD 8.88). Only three participants had lost no teeth and 10.7% were completely edentulous. Participants who used tamoxifen for more than 1 year had a higher mean missing teeth (13.99 vs. 10.45; $P = 0.030$). After the adjustments, the occurrence of more than 12 missing teeth was 2.75-fold higher among women who used tamoxifen for more than 1 year (95% CI: 1.06–7.12). Moreover, age over 65 years, referral for treatment by the public healthcare system, less use of dental services, xerostomia and a lower occurrence of dental caries remained associated with the loss of more than 12 teeth.

Conclusion

Longer use of tamoxifen was associated with greater tooth loss in breast cancer survivors.

Clinical relevance:

Based on estimates of the increase in cases of breast cancer, the prolonged use of tamoxifen for the treatment of this disease can exert an impact on oral health through the occurrence of tooth loss. These findings can contribute to the planning and implementation of oral health care and prevention strategies for such patients.

Introduction

Despite major improvements in oral health throughout the world, problems remain, particularly in less privileged populations. Dental caries, periodontal disease and tooth loss (TL) are major public health problems [1]. TL is associated with age, smoking, alcohol consumption, socioeconomic status and poor

nutrition. Moreover, caries and periodontal disease are progressive processes that can lead to TL if not treated adequately [2]. Functional impairment stemming from TL exerts an influence on the type of food ingested and, consequently, nutritional intake. Depending on its location, TL can cause dissatisfaction with one's appearance and exert a negative impact on quality of life [3].

Breast cancer (BC) is an important public health problem. Global estimates indicate that it is the second most common form of cancer in the world and the most incident cancer among women, accounting for 24% of all cases cancer in 2018, with approximately 2.1 million new cases. BC is the fifth leading cause of death due to cancer and the most frequent cause of death by cancer in women, especially in less developed regions [4]. Certain risk factors have become more common in the population, such as those related to menstruation (early age of menarche and advanced age of menopause), reproduction (nulliparity, late age at first birth and fewer children), exogenous hormone intake (use of oral contraceptives and hormone replacement therapy), nutrition (alcohol consumption) and anthropometric characteristics (greater weight, weight gain in adult life and distribution of body fat), whereas breastfeeding and physical activity are considered protection factors [5, 6].

The choice of treatment for BC is complex and based on factors related to the type of tumor, stage of the disease and the prognosis [7]. For hormone receptor positive tumors, the American Cancer Society recommends the use of antiestrogen therapy for five to ten years, with tamoxifen or aromatase inhibitors (AIs) to reduce the risk of the recurrence and improve overall survival [8]. However, therapies for BC are associated with acute or late-onset oral complications, such as mucositis, pain, xerostomia, dental caries, osteoradionecrosis, changes in periodontal tissues, oral lesions, neurosensory changes and changes in the sense of taste [9, 10]. Such dental problems have a negative impact on oral health-related quality of life in this population [11]. A recent study showed that AIs negatively affected tooth loss and attachment loss, while tamoxifen did not affect dental condition in women with breast cancer [12]. To our knowledge, no study has associated tamoxifen with tooth loss, controlling for confounding variables. There is also concern regarding the occurrence of acute dental infection while patients are undergoing oncological treatment, as it is possible for a secondary odontogenic infection to become a systemic infection, which would result in an aggravation of the patient's health status. Thus, a dental examination and the treatment of existing conditions are warranted prior to undergoing cancer therapy. Due to the patient's vulnerability, the dentist may opt for less conservative treatment, such as tooth extraction, to eliminate focal infections [13].

Based on the aspects described above, we hypothesized that the systemic and local effect of tamoxifen could lead to an increase in the occurrence of TL among BC survivors. Therefore, the aim of the present study was to investigate the association between duration of tamoxifen use and tooth loss, adjusting for confounding variables.

Methods

Study design

A cross-sectional study was conducted at a hospital in southern Brazil. Data collection was performed from January to August 2017. Eligible participants were women with BC older than 18 years of age undergoing oncological treatment. Patients who did not sign the statement of informed consent were excluded. This study received approval from the human research ethics committee of *Universidade Franciscana*.

Sample

The sample size was determined using data from a study comparing oral health-related quality of life (OHRQoL) between women with and without BC. The difference in the OHRQoL score was used for the calculation (mean \pm SD: 1.28 ± 0.53 and 1.02 ± 0.11 , respectively) [14]. A minimum of 80 participants was estimated. The sample size was increased to 120 participants considering the multivariate analysis and to compensate for a possible 30% dropout rate. This sample is compatible with the expected 25% higher rate of tooth loss in patients with BC [15]. For a study power of 80%, 5% significance level and a two-tailed hypothesis test, at least 116 participants were required.

Evaluations instruments

Interview

Interviews were held with the aid of a structured questionnaire to collect information on sociodemographic characteristics (age, race, schooling and income), medical history (diagnosis, BC staging, radiotherapy, chemotherapy and tamoxifen use), origin of referral for BC treatment, tobacco consumption and the use of dental services. Three trained interviewers administered the questionnaires to the participants.

Dental evaluation

Oral examinations were performed in a room with natural light, common chair and cotton rolls. TL was evaluated using the M component of the Decayed, Missing and Filled Teeth (DMFT) index [16]. A tooth was considered present in the mouth when any part of its structure was visible.

The evaluations were performed by a single examiner who had previously undergone training and calibration exercises for the use of the DMFT index. The training process was coordinated by an experienced dentist until there was satisfactory inter-examiner agreement regarding the DMFT parameters. The examiner then evaluated 15 individuals and repeated the analysis in random order after at least one hour, obtaining a Kappa coefficient of 0.97 for intra-examiner agreement.

Statistical analysis

The data were analyzed with the aid of the Statistical Package for the Social Sciences (SPSS 22, Chicago, USA). TL was the primary outcome and was dichotomized by mean (\leq or $>$ 12 lost teeth). The categorized independent variables were age (\leq or $>$ 65 years), schooling (\leq or $>$ nine years), family income [$<$ or \geq the Brazilian monthly minimum wage (BMMW = US\$181.34 at the time of the study)],

origin of medical referral for BC treatment (Brazilian public healthcare system or private healthcare system), BC diagnosis (invasive ductal carcinoma or other), BC staging (I-II or III-IV), radiotherapy (yes or no), chemotherapy (yes or no), tamoxifen time of use (\leq or $>$ 1 year), use of dental services (\leq or $>$ 1 year), xerostomia (no or yes) and untreated dental caries [\leq or $>$ one carious teeth (based on DMFT index)]. The significance level was set at 5% and the power of the study was 80%. Descriptive and unadjusted analyses were performed to determine associations between the independent variables and the outcome. The Mann-Whitney was used to assess the association between independent variables and tooth loss. Logistic regression models were run to determine the strength of the associations, with the calculation of odds ratios (OR) and 95% confidence intervals (CI). All variables with a value of P-value $<$ 0.05 in the bivariate analysis were incorporated into the multivariate model. Variables with a p-value $<$ 0.05 in the final model were considered significantly associated with the outcome.

Results

A total of 140 women with BC were evaluated. The response rate was 76.9% (140/182). The losses were due to the public transportation schedule (25 women) and refusal to participate (seven women). Nine women who were taking an aromatase inhibitor and one who was not taking hormone therapy were excluded. The mean age of the participants was 56.67 years (SD: 10.96). The majority had less than nine years of schooling (67.1%), had a family income higher than the BMMW (63.6%) and had been referred to oncological treatment by the public healthcare system (77.1%). Smaller proportions of the women were diagnosed with a type of cancer other than invasive ductal carcinoma (18.7%), had tumors in stages III and IV (15.9%) and did not undergo radiotherapy (33.6%). Among the “other types” of BC, invasive lobular carcinoma accounted for the largest proportion (9.3%), whereas the remaining cases were distributed among nine less common types. All participants used tamoxifen, being 69.3% for more than 12 months. As for oral health, 56.8% had used dental services for more than 12 months, 70.7% and 27.9% had xerostomia and more than one tooth with untreated dental caries (Table 1).

Table 1
 Characteristics of study participants (n = 140)

	N	%
Age (years)	56.67	10.96
Mean ± SD		
Schooling (years)		
≤ 9	94	67.1
> 9	46	32.9
Family income (BMMW)		
< 1	51	36.4
≥ 1	89	63.6
Origin of medical referral		
Public health system	108	77.1
Private health system	32	22.9
BC diagnosis		
Invasive ductal carcinoma	113	81.3
Others	26	18.7
Time since diagnosis	37.30	20.62
Mean ± SD (months)		
BC staging		
I-II	116	84.1
III-IV	22	15.9
Radiotherapy		
No	47	33.6
Yes	93	66.4
Chemotherapy		
No	61	43.6
Yes	79	56.4

BMMW: Brazilian monthly minimum wage; BC: breast cancer

	N	%
Duration of tamoxifen (year)		
≤ 1	43	30.7
> 1	97	69.3
Use of dental services (year)		
≤ 1	60	43.2
> 1	79	56.8
Xerostomia		
No	41	29.3
Yes	99	70.7
Untreated dental caries		
≤ 1	101	72.1
> 1	39	27.9
Tooth loss		
Mean ± SD	12.96	8.88
BMMW: Brazilian monthly minimum wage; BC: breast cancer		

Only three participants had lost no teeth and 10.7% were completely edentulous. The mean of missing teeth was 12.96 (SD 8.88). The number of missing teeth was significantly higher among women who had used tamoxifen for more than 1 year (mean: 13.99 ± 8.78) than among those who used it for a shorter time (mean: 10.45 ± 8.77) (P = 0.030). In addition, participants age over 65 years, less than 9 years of study, referred by the public healthcare system, less use of dental services, with xerostomia and lower occurrence of untreated dental caries had higher means of missing teeth (P < 0.05) (Table 2). A total of 42.9% of the sample had more than 12 missing teeth. In the crude model, TL was associated with demographic/socioeconomic variables, oral health and tamoxifen therapy. After the adjustments for possible confounders, the occurrence of more than 12 missing teeth was 2.75-fold higher among women who took tamoxifen for more than 1 year (95% CI: 1.06 to 7.12) compared to those who took it for less than 1 year. Moreover, age over 65 years, referral by the public healthcare system, less use of dental services, with xerostomia and a lower occurrence of dental caries remained associated with missing more than 12 teeth (P < 0.05) (Table 3). Additional analyzes demonstrated that inclusion in the xerostomia adjustment reduced the measure of effect of tamoxifen duration on tooth loss from 2.99 (P = 0.021) to 2.74 (P = 0.038), suggesting that at least part of the effect of tamoxifen on tooth loss it was mediated by the increased perception of dry mouth.

Table 2

Tooth loss according to demographic/socioeconomic characteristic, oral health and tamoxifen therapy (n = 140).

	Tooth loss	P*
	Mean ± SD	
Age (years)		< 0.001
≤ 65	10.87 ± 8.36	
> 65	18.78 ± 7.81	
Schooling (years)		0.002
≤ 9	14.59 ± 8.77	
> 9	9.65 ± 8.25	
Origin of medical referral		0.014
Public health system	14.02 ± 9.06	
Private health system	9.41 ± 7.31	
Duration of tamoxifen (year)		0.030
≤ 1	10.45 ± 8.77	
> 1	13.99 ± 8.78	
Use of dental services (year)		0.001
≤ 1	9.95 ± 7.92	
> 1	15.18 ± 8.98	
Xerostomia		0.002
No	9.07 ± 7.06	
Yes	14.58 ± 9.09	
Untreated dental caries		0.032
≤ 1	13.91 ± 9.44	
> 1	10.38 ± 6.81	
*Mann-Whitney test		

Table 3

Crude and adjusted analysis of associations between independent variables and tooth loss (n = 140)

	N	> 12 Missing Teeth n (%)	OR (CI 95%) Crude	P	OR (CI 95%) Adjusted	P
Age (years)				< 0.001		0.008
≤ 65	104	35 (33.7)	1.0		1.0	
> 65	36	25 (69.4)	4.48 (1.98–10.15)		3.54 (1.39–9.03)	
Schooling (years)				0.016		0.156
≤ 9	94	47 (50.0)	2.54 (1.19–5.42)		1.94 (0.78–4.83)	
> 9	46	13 (28.3)	1.0		1.0	
Origin of medical referral				0.23		0.027
Public health system	108	52 (48.1)	1.0		1.0	
Private health system	32	8 (25.0)	0.36 (0.15–0.87)		0.30 (0.10–0.87)	
Duration of tamoxifen (year)				0.019		0.038
≤ 1	43	12 (27.9)	1.0		1.0	
> 1	97	48 (49.5)	2.53 (1.16–5.50)		2.75 (1.06–7.12)	
Use of dental services (year)				0.001		0.008
≤ 1	60	16 (26.7)	1.0		1.0	
> 1	79	43 (54.4)	3.29 (1.59–6.77)		3.21 (1.35–7.65)	
Xerostomia				< 0.001		0.025
No	41	8 (19.5)	1.0		1.0	

OR, odds ratio; CI, confidence interval (logistic regression analysis)

	N	> 12 Missing Teeth n (%)	OR (CI 95%) Crude	P	OR (CI 95%) Adjusted	P
Yes	99	52 (52.5)	4.56 (1.92– 10.86)		3.12 (1.16–8.40)	
Untreated dental caries				0.032		0.008
≤ 1	101	49 (48.5)	1.0		1.0	
> 1	39	11 (28.2)	0.43 (0.20– 0.93)		0.25 (0.09–0.70)	
OR, odds ratio; CI, confidence interval (logistic regression analysis)						

Discussion

Tooth loss is one of the most prevalent oral health problems [1]. It can determine social inequality as well as feeding and phonation difficulties and, depending on the location, can affect the esthetics of the smile [3]. Moreover, increased tooth loss was negatively associated with the quality of diet and nutrition [17]. Thus, this outcome exerts a strong impact on quality of life [3] and is considerable public health problem. Breast cancer is the second most common type of cancer and the primary form of cancer among women [4]. In the present study, older age, referral from the public healthcare system, lower occurrence of dental caries, less use of dental services, xerostomia and taking tamoxifen for more than 1 year were associated with a greater occurrence of TL among BC survivors.

Meta-analyses have revealed an association between TL and a greater risk of some types of cancer due to plausible pathways [18, 19]. In most cases, TL is a consequence of periodontal disease and dental caries as well as the complications of these conditions, such as pulp involvement [2]. Both diseases trigger a local inflammatory response that can have systemic repercussions [20] and the relationship between inflammation and cancer is well recognized [21]. The stimulation of chronic inflammation can lead the organism to produce pro-inflammatory cytokines, such as interleukin (IL) 1, 2 and 8. Cells induced by the mutation of the cyclooxygenase-2 gene activate proto-oncogenes and inhibit the expression of tumor suppressor genes, leading to the occurrence of BC [22, 23].

Tamoxifen is part of hormone therapy for BC, the cells of which are hormone receptor positive. This drug is a selective estrogen receptor modulator that inhibits the binding of estrogen to receptors on tumor cells [24]. The standard duration of hormone therapy for BC is five years but can be extended for another five years [24, 25]. Considering this long duration and exposure to hormone therapy, understanding the side

effects is crucial to better planning on the part of dentists to ensure good long-term oral health for these patients.

In the present study, the length of treatment remained associated with the outcome even after the adjustments for the main predictors, as TL was significantly more prevalent among the women who had taken tamoxifen for more than one year. However, the few studies addressing the effects of this drug on the oral health of BC survivors offer conflicting results. Estrogen deficiency has been associated with reduced salivary flow and lower salivary pH [26]. Medications that reduce estrogen levels, such as tamoxifen, can affect periodontal health and reduce salivary flow in patients with BC [27]. Dentists who treated women with breast cancer taking estrogen receptor inhibitors reported that the most common complaints were an increase in gingival inflammation, gingival bleeding, xerostomia and a burning sensation in soft tissues [28]. Saliva plays a key role in maintaining oral health and both quantitative and qualitative changes in saliva can affect oral homeostasis [29]. Studies have shown that oral tissues are sensitive to the effects of estrogen and that estrogens can regulate salivary physiology, but the mechanism by which estrogens modulate salivary gland function is still not well understood [30]. The expression of estrogen receptors, specifically β receptors, in both mucosal and serous acinar and ductal cells of minor salivary, parotid and submandibular glands has been described, suggesting that estrogens can directly regulate salivary gland function [30]. A recently published study demonstrated that low estrogen levels influenced the microbial composition of the oral cavity in rats, increasing the amount of bacteria in the saliva and, therefore, contributing to the progression of periapical lesions [31]. Similarly, to the action of tamoxifen on mammary gland tissue (inhibition of estrogen receptors), this drug seems to exert the same effect on the salivary glands, inhibiting estrogen receptors and affecting the secretion and composition of saliva. This could explain the present findings. Most participants in the present study experienced xerostomia, which was associated with tooth loss. Hyposalivation can lead to an increased occurrence of gingival inflammation, dental caries, clinical attachment loss and, consequently, tooth loss [32, 33].

A lower occurrence of dental caries was associated with the loss of more than 12 teeth, which is in disagreement with data described in the literature [34]. We may raise a hypothesis for this result: dentists may have opted for the extraction of teeth with caries to remove any possible infection site or for not having sufficient time for less invasive procedures prior to oncological treatment [13]. An older age was also associated with the risk of having more than 12 lost teeth. This may be explained by the increased risk of periodontitis with age, as this disease affects more than 50% of individuals over 50 years of age. Indeed, meta-analysis on TL in general determined an increase in the prevalence of TL with age [1].

Referrals for oncological treatment made by the Brazilian public healthcare system and the lower use of dental services were also associated with TL. These findings may be explained by social inequalities, difficulty in gaining access to restorative treatment and the more common occurrence of mutilating dental practices (extractions) in the public healthcare system [35], as the patients referred by the public healthcare system likely also use this system for their oral health needs. A study conducted with users of the Brazilian public healthcare system found that TL is considered "normal" and "expected" [36].

Moreover, women referred by private healthcare services may have a greater frequency of dental appointments because they also seek private dental services. Indeed, it is common for groups with a higher income to use dental services more and have better oral health [37].

Some methodological weaknesses of the present study need to be addressed. First, we did not investigate periodontal variables as predictors of a higher occurrence of TL because we did not have a suitable place to collect such data. Second, the cross-sectional design does not enable the establishment of causal relationships. Third, the sample had specific characteristics of the instate region of southern Brazil and, therefore, the data should be generalized to similar populations. Moreover, one should bear in mind that reference centers concentrate a higher frequency of diseases. Longitudinal studies should be performed with different populations to confirm the present findings.

Conclusion

Beside demographic/socioeconomic characteristics, oral factors and referrals made by the public healthcare system, the use of tamoxifen for more than one year was associated with greater tooth loss among breast cancer survivors. The present findings underscore the importance of understanding factors associated with greater tooth loss in this population to assist in the planning and decision making of dentists as well as the planning of actions at healthcare service with the aim of reducing the occurrence of oral problems in breast cancer survivors.

Declarations

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical aspects This study received approval from the human research ethics committee of *Universidade Franciscana* (certificate number: 1.876.689), and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent All participants signed a statement of informed consent.

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