RSBO

ISSN:
Electronic version: 1984-5685
RSBO. 2023 Jan-Jun;20(1):25-30

Original Research Article

Cancer treatment with hormone therapy and its relationship with xerostomia and hyposalivation

Gláucia Helena Faraco de Medeiros[1]
Jheiniffer Folchinhi[2]
Daniela Daufenback Pompeo[2]
Jefferson Ricardo Pereira[3]

Corresponding author:
Gláucia Helena Faraco de Medeiros
Av. José Acácio Moreira, n. 787 – Dehon
CEP 88704-900 – Tubarão –SC – Brasil
E-mail: gaufaraco@gmail.com

[1] Dentistry Course, University of Southern Santa Catarina – Tubarão – SC – Brazil.
[2] Dentist – Tubarão – SC – Brazil.
[3] Graduate Program in Health Sciences, University of Southern Santa Catarina – Tubarão – SC – Brazil.

Received for publication: February 8, 2022. Accepted for publication: September 23, 2022.

Keywords:
breast neoplasms; women; xerostomia; hyposalivation antineoplastic agents.

Abstract

Introduction: The appearance of new drugs for cancer treatment has increased patient survival but it has also brought adverse effects, such as the sensation of dry mouth and hyposalivation **Objective:** To assess the relationship of using hormone therapy in breast and prostate cancer patients and the occurrence of xerostomia and hyposalivation. **Material and methods:** Cross-sectional study with 114 patients diagnosed with cancer and treated with hormone therapy. The researcher collected resting and stimulated salivary flows in the morning. The descriptive statistic analysis, chi-square test ($p<0.005$), and t-test (<0.005) were performed using the Statistical Package for Social Science™ (SSPS), version 21, for different variables of hyposalivation and hormone therapy. **Results:** The results showed that 67 (55.8%) patients using hormone therapy drugs presented hyposalivation and 73 (64%) patients presented xerostomia. **Conclusion:** According to the results of this study, there is a positive association between stimulated hyposalivation and the use of hormone therapy drugs ($p = 0.015$). There was also a positive association between hyposalivation and xerostomia and the use of hormone therapy drugs ($p = 0.049$ and $p = 0.001$).

Introduction

Cancer treatment should start from the moment the patient receives a confirmed diagnosis and it involves a series of multi-professional interventions including surgery, radiotherapy, chemotherapy, hormone therapy, and target therapy. For cases treated with hormone therapy, the main drugs used to treat breast cancer are tamoxifen (TMXO), when there are estrogen receptors in the tumor mass that inhibit its production; and anastrozole, an aromatase inhibitor (AI) that also works on estrogen in postmenopausal women. For the condition of prostate cancer, the hormone therapy drug bicalutamide works by inhibiting androgenic hormones [5, 6, 18]. Choosing one medication over another is determined, among other factors, by the type and stage of the tumor. While using tamoxifen is recommended to premenopausal women, postmenopausal women may use both tamoxifen and anastrozole [18] Bicalutamide has been indicated by the FDA for the metastatic treatment of prostate cancer [5]. When administered orally, its action may be affected by the concomitant use of other drugs and cause adverse effects in the oral cavity.

Studies have shown that estrogen is important for the maintenance of bone and soft tissues in the oral cavity. Thus, drugs that affect the production and prevent or complicate the connection of estrogen to its receptors, such as anastrozole, may affect bone and soft tissues in the oral cavity, increase the risk of periodontal disease, change the taste, decrease salivary flow, and cause xerostomia [6, 18].

Xerostomia is characterized by the sensation of dry mouth and it may be primary or secondary. Primary xerostomia is characterized by the decrease in resting or stimulated saliva production, and secondary xerostomia is characterized by the dryness of the mouth with the absence of changes in salivary flow. Xerostomia and changed salivary flow may occur from changes in saliva composition, radiation in the head and neck region, smoking habit, alcoholism, and excess coffee intake, which are among the local factors that may lead to xerostomia [1, 2, 4, 13, 20].

Patients with xerostomia may find it difficult to eat and/or speak and present a burning sensation, halitosis, and change in taste. Lip dryness, oral candidosis, and dental caries may also be present even if the patient has good oral hygiene. Identifying the etiological factor early and consequently determining the diagnosis, either primary or secondary, will allow introducing a better and more effective treatment plan aiming at control and comfort, especially to women older than 60 years [1, 2, 13].

The literature is scarce on the relationship between xerostomia and/or hyposalivation and the use of hormone therapy drugs. As for the use of bicalutamide for patients with prostate cancer, there are no studies available. The studies related to the use of anastrozole are not specific for this condition. They assess changes in the oral cavity as a whole and do not determine in what treatment phase it is more frequently found [4, 16, 18].

In the specific case of estrogen receptors, studies have evidenced that the presence of this hormone in the oral mucosa and salivary glands, as well as an antagonist action to this hormone, may be responsible for the sensation of dry mouth [11, 18, 19]. Preliminary results of a pilot study performed by Taichman *et al.* [18] did not show differences between the perception of dry mouth or decreased salivary flow of patients using aromatase inhibitors and patients without the medication. However, a longitudinal study performed by the same authors [19], published in 2016, warns about the long-term decrease in salivary flow due to the use of aromatase inhibitors, highlighting that further studies should be performed aiming at these patients with a higher need for oral health care.

Therefore, this research hypothesizes that anastrozole and bicalutamide used in the treatment of breast and prostate cancers, respectively, cause changes in salivary flow and the presence of xerostomia. This study aimed to assess the relationship of xerostomia and hyposalivation with the use of hormone therapy drugs in patients subjected to oncological treatment, by measuring salivary flow.

Material and methods

The present research was an observational, epidemiological, and cross-sectional study. The sample was calculated with the OpenEpi™ 3.01 software, (n = [EDFF*Np(1-p)]/ [$(d^2/Z^2_{1-\alpha/2}$*(N-1)+p*(1-p)], considering a 95% confidence interval, 5% confidence level, minimum sample of 132 patients, and 82% sample power. The inclusion criteria were patients aged 18 years or older, subjected to hormone therapy with anastrozole or bicalutamide to treat breast or prostate cancers, respectively, at the Oncology Outpatient Unit of the Nossa Senhora da Conceição Hospital (Tubarão, Santa Catarina, Brazil). The participants were invited to participate in the study and accepted the Informed Consent Form. The procedure of

random sampling by convenience was used. The data were collected from July to October 2016. The Research Ethics Committee of the University of Southern Santa Catarina approved the project, under CAAE number 57324716.2.0000.5369, report number 1.619.905.

Sociodemographic data such as age, sex, type of cancer, therapy used, and other medications used were obtained with a self-filled questionnaire. The patients also answered (yes or no) to questions on the sensation of dry mouth, lip dryness, and amount of saliva they believed having (a lot or little). The salivary flow was assessed with the methodology proposed by Sreebny and Valdini [17]. Saliva was collected at two moments: resting and stimulated. To collect resting saliva, the patient was asked to sit comfortably and expel saliva in a plastic cup for six continuous minutes. Stimulated saliva was collected by chewing a piece of sterile latex with 3 mm of thickness and 1 cm of length, tied by a dental floss to avoid swallowing. The saliva produced was deposited in another plastic cup also for six minutes. After a resting period to reduce the interference of foam, aided by a disposable 10-ml syringe, the salivary flow was quantified in millimeters and divided by six to obtain values in ml/min, considering resting hyposalivation values ≤ 0.1 ml/min and ≤ 0.7 ml/min when stimulated. The values were written down on their respective questionnaires.

The data collected were inserted in the Statistical Package for Social Science™ (SSPS), version 15.0, for the descriptive analysis of data normality and statistical inference to determine the mean, standard deviation, and mean standard error. The chi-square test was used to verify the association of variables and the Student's t-test was performed to identify the difference of means between the different groups. The results were considered statistically significant at p-value < 0.05.

Results

Eighteen patients were excluded from the sample for dropping out during the collection period, resulting in a sample of 114 participants at 76.81% test power. From the 114 patients included in the sample, 16 (14%) were men diagnosed with prostate cancer who used bicalutamide and 98 (86%) were women diagnosed with breast cancer who used anastrozole. The average age was 64.88 (EP +/- 0.87) years, whereas the minimum age was 43 years and the maximum age was 86 years.

Besides antineoplastic drugs, 92 patients (80.7%) used some other medication, especially for cardiovascular diseases or mental disorders. These medications were used before cancer treatment by 70 (76.1%) patients. Table I shows the association between the presence of xerostomia reported by patients, before and after starting hormone therapy. The chi-square test presented a statistically significant result (p=0.005).

Table I – Distribution of xerostomia reported by patients before and after hormone therapy $Test - \chi^2$

Xerostomia before hormone therapy	Xerostomia after hormone therapy p=0.005 Population n= 114 n (%)	
	Present	Absent
Present	19 (16.7)	2 (1.8)
Absent	54 (47.4)	39 (34.2)
Total	73 (64)	41 (36)

Decreased resting salivary flow was observed in 65 (85.1%) patients and stimulated salivary flow was observed in 97 (85.1%) patients. The mean resting salivary flow volume for the patients using anastrozole was 0.13 ml/min (EP ± 0.12), while the mean stimulated salivary flow volume was 0.51 ml/min (EP ± 0.35). In patients using bicalutamide, the mean resting salivary flow volume was 0.24 ml/min (EP ± 0.70), while the mean stimulated salivary flow volume was 0.97 ml/min (EP ± 0.23). The stimulated salivary flow volume presented a statistically significant result between the different groups; p = 0.0001 (CI: -0.0/0.05).

Table II shows the association between the type of hormone therapy drugs used and the presence of resting hyposalivation and stimulated hyposalivation, revealing a statistically significant result for stimulated hyposalivation (p=0.015).

Table II – Association among hormone therapy and rest and stimulated hyposalivation $Teste - \chi^2$

Hormone therapy	Unstimulated salivary p= 0.65 Population n= 114 n (%)		Stimulated hyposalivation p= 0.015 Population n= 114 n (%)	
	Absent	Present	Absent	Present
Anastrozole	43 (43.9)	55 (56.1)	87 (88.8)	11 (11.2)
Bicalutamide	8 (50)	8 (50)	10 (62.5)	6 (37.5)
Total	51 (44.7)	63 (55.3)	97 (51.1)	17 (14.9)

When considering the association between the use of hormone therapy drugs, the presence of hyposalivation regardless of salivary flow stimulus, and the presence of xerostomia, the $Test - \chi^2$ presented a statistically significant result (p = 0.049; p = 0.001, respectively), as shown in table III.

Table III – Association between hyposalivation and hormone therapy $Test - \chi^2$

Hormone therapy	Hyposalivation p= 0.049 Population n= 114 n (%)		Xerostomia p= 0.001 Population n= 114 n (%)	
	Absent	Present	Absent	Present
Anastrozole	44 (49.9)	54 (55.1)	29 (29. 6)	69 (70.4)
Bicalutamide	3 (18.8)	13 (81.3)	12 (75.0)	4 (25.0)
Total	47 (41.2)	67 (55.8)	41 (36.0)	73 (64.0)

Discussion

Considering the results found in this study, there is a significant change in salivary flow and the presence of xerostomia in patients under cancer treatment.

The high rate of patients using other medications than the ones for cancer treatment reflects the global perspective, which shows a high incidence and prevalence rates of chronic non-transmissible diseases such as cardiovascular diseases and mental disorders, among which are depression and anxiety [4, 21]. Johanson *et al.* [9] highlight the xerostomic potential and salivary changes of these medications. Although the salivary flow tests have been performed only once along with the use of hormone therapy drugs, it is not possible to confirm that changes in salivary flow and xerostomia already existed before the antineoplastic treatment or whether they were potentiated by the association of the additional medication. Longitudinal studies are suggested for a better assessment of this association.

The mean resting salivary flow volume found in this study was higher than the value found by Niklander *et al.* [14] (0.1 ± 0.28 ml/min), which shows no functional changes in salivary glands. The means of stimulated salivary flow volume are similar to the values obtained by Rahnama *et al.* [15] (0.812 ± 0.095 ml/min). Lago *et al.* [10] observed that hormone therapy increases salivary flow in 0.52 ml/min, showing an influence of hormone therapy drugs used by postmenopausal women, especially the ones under estroprogestative

therapy. This study did not aim to assess whether women were pre- or postmenopausal, but it allows inferring that these drugs work on the salivary glands and affect salivary flow.

Aromatase inhibitors such as anastrozole have become the hormone therapy drug of choice for the treatment of breast cancer in postmenopausal women because they inhibit the production of estrogen, reducing the growth of cancer and preventing recurrences. Decreased salivary flow is among the side effects, with either stimulus or not [18] which is also evidenced in the present study. Studies such as by Foschini *et al*., in 2017 [7], showed the presence of estrogen receptors in salivary gland tumors, revealing the presence of this hormone in the mucosa of the glands. The decrease in estrogen production due to hormone therapy drugs may lead to decreased salivary production, resulting in a hyposalivation condition.

A study has evidenced a decrease in androgenic hormone in menopausal women and that this condition is a predisposing factor for Sjögren syndrome [3]. This research is the first study assessing the association between the use of hormone therapy drugs with antiandrogenic action, hyposalivation, and xerostomia, although it has shown a statistically significant result for hyposalivation in the presence of stimulated salivary flow, xerostomia, and hyposalivation. Although prostate cancer is the second most frequently found in men, its incidence and prevalence are lower than breast cancer in women [18]. Moreover, the use of hormone therapy drugs, such as the ones that inhibit the androgenic synthesis, is indicated only in cases of metastasis [5]. Both these conditions may justify the presence of only 16 patients in the sample. The decrease or absence of the androgenic hormone in these patients by the action of hormone therapy drugs may be responsible for the changes found in salivary flow. However, further studies are suggested to better understand this condition.

The sensation of dry mouth in this study was determined by patient self-perception. It is known that the symptom differs from one person to another and the absence of standardization for the responses may have under- or overestimated the results found. This same limitation was also observed in other studies [3, 22], which showed a relationship between xerostomia and different oncological diseases, with a strong relationship between head and neck radiotherapy and women older than 60 years [2, 4].

Although studies recommend a mean time to collect resting and stimulated saliva of five minutes, Löfgren *et al*. [12] addressed, in a systematic review, diagnostic methods of mouth dryness and salivary gland function. The results showed that increasing the time increased the specificity of salivary flow reduction. It also stands out that the methods to assess mouth dryness are scarce and show methodological deficiencies. In this study, the salivary flow was collected for six minutes due to a misguided interpretation of the methodology used, in which the first minute of each collection was interpreted as a preparation minute and added to the total collection time. To prevent underestimating the salivary volume, this minute was added in the methodology, so the total volume was divided by six minutes in both resting and stimulated salivary flows.

Even with limitations, such as the absence of information on salivary flow and xerostomia before the treatment and during it, absence of a control group, and decreased sample power for not reaching the minimum sample number, the results obtained in this study showed the presence of hyposalivation and xerostomia in patients under hormone therapy and that this condition affects or aggravates the quality of life. The magnitude of this response was approximately four times higher in men than in women. Considering the small sample size and the heterogeneous population, further studies are suggested to better explain the relationship between hyposalivation, xerostomia, and hormone therapy.

Conclusion

The results of this study allow concluding that:

- Anastrozole and bicalutamide presented a statistically significant result for mean stimulated salivary flow volume; p = 0.0001 (CI: -0.70/-0.205).
- Anastrozole and bicalutamide cause a statistically significant decrease in stimulated hyposalivation (p = 0.049).
- Xerostomia is a usual complaint among patients using anastrozole and bicalutamide, showing a statistically significant result (p = 0.001).

References

1. AAOM Clinical Practice Statement: Subject: Clinical management of cancer therapy – induced salivary gland hypofunction and xerostomia. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016 Sep;122(3):310-2.

2. Astrom AN, Lie SA, Ekbacj G, Gulcan F, Ordell S. Self- reported dry mouth among ageing people: a longitudinal, cross-national study. Eur J Oral Sci. 2019 Apr;127(2):130-8.

3. Baharvand M, Khodadoustan A, Mohammad M, Mortazavi H, Movahhedlan A. Xerostomia due to systemic disease: a review of 20 conditions and mechanisms. Ann Med Health Sci Res. 2014 Jul;4(4):503-10.

4. Barbe AG. Medication -induced xerostomia and hyposalivation in the elderly: culprits, complications, and management. Drugs & Aging. 2018 Oct;35(10):877-85.

5. Beebe-Dimmer JL, Rueterbusch JJ, Bylsma LC, Gillezeau C, Fryzek J, Schultz NM et al. Patterns of Bicalutamide use in prostate cancer treatment: A U.S. Real-Word analysis using the SEER – Medicare Database. Adv Ther. 2018 Sep;35(9):1438-51.

6. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in Globocan 2012. Int J Cancer. 2015;136(5):E359-86.

7. Foschini MP, Morandi L, Asioli S, Giove G, Corradini AG, Eusebi V. The morphological spectrum of salivary gland type tumours of the breast. Pathology. 2017 Feb; 49(2):215-27.

8. Hanchanale S, Adkinson L, Daniel S, Fleming M, Oxberry SG. Systematic literature review: xerostomia in advanced cancer patients. Support Care Cancer. 2015 Mar;23(3):881-8.

9. Johanson CN, Osterberg T, Lernfelt B, Ekstrom J, Birkherd D. Salivary secretion and drug treatment in four 70-year-old Swedish cohorts during a period of 30 years. Gerodontology. 2015 Sep;32(3):202-10.

10. Lago ML, Oliveira AE, Lopes FF, Ferreira EB, Rodrigues VP, Brito LM. The influence of hormone replacement therapy on the salivary flow of post-menopausal women. Gynecol Endocrinol. 2015 Feb;31(2):109-12.

11. Liu S, Niu K, Da Y, Liu Y, Zhang J, Wang W et al Effects of standardized isopropanolic black cohosh and estrogen on salivary function in ovariectomized rats. Biomed Pharmother. 2018 Jan;97:1438-44.

12. Löfgren CD, Wickström C, Sonesson M, Lagunas PT, Christersson C. A systematic review of methods to diagnose oral dryness and salivary gland function. BMC Oral Health. 2012 Aug;12:29.

13. Millsop JW, Wang EA, Fazel N. Etiology, evaluation and management of xerostomia. Clin Dermatol. 2017 Sep-Oct;35(5):468-76.

14. Niklander S, Veas L, Barrera C, Fuentes F, Chiappini G, Marshall M. Risk factors, hyposalivation and impact of xerostomia on oral health-related quality of life. Braz Oral Res. 2017 Jan;31:e14.

15. Rahnama, M, Madej-Czerwonka B, Jastrzebska-Jamrogiewicz I, Jamrogiewicz R. Analysis of the influence of parenteral cancer chemotherapy on the health condition oral mucosa. Contemp Oncol (Pozn). 2015 Mar;19(1):77-8.

16. Sözeri E, Kutlutürkan S. Taste alteration in patients receiving chemotherapy. J Breast Health. 2015 Apr;11(2):81-7.

17. Sreebny LM, Valdini A, Yu A. Xerostomia. Part II: relationship to nonoral symptoms drugs and diseases. Oral Surg Oral Med Oral Pathol. 1989 Oct;68(4):419-27.

18. Taichman LS, Inglehart MR, Giannobile WV, Braun T, Kolenic G, Poznak VC. Periodontal health in women with early -stage postmenoaousal breast cancer newly on aromatase inhibitors: a pilot study. J Peridontol. 2015 Jul;86(7):906-16.

19. Taichman LS, Van Poznak CH, Inglehart MR. Self-reported oral health and quality of life of postmenopausal breast cancer survivors on aromatase inhibitors and women without cancer diagnoses: a longitudinal analysis. Support Care Cancer. 2016 Nov;24(11):4815-24.

20. Tanasiewicz M, Hildebrandt T, Oberztyn I, Xeorostomia of various etiologies: a review of the literature. Adv Clin Exp Med. 2016 Jan-Feb;25(1):199-206.

21. Turner MD. Hyposalivation and xerostomia: etiology, complications, and medical management. Dent Clin North Am. 2016 Apr;60(2):435-43.

22. Wilberg P, Hjermstad MJ, Ottesen S, Herlofson BB. Oral health is an important issue in end-of-life cancer care. Support Care Cancer. 2012 Dec;20(12):3115-22.