Received: 24 January 2022 | Revised: 15 July 2022 | Accepted: 18 July 2022

DOI: 10.1002/hsr2.783

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Nighttime salivary cortisol as a biomarker of stress and an indicator of worsening quality of life in patients with head and neck cancer: A cross-sectional study

Marla S. P. Cruz[1] | Tercio G. Reis[2] | Antoniel C. Oliveira[3] | Marluce M. Macedo[3] | José de Bessa[1] | Márcio C. Oliveira[1]

[1]Departament of Public Health/Epidemiology, State University of Feira de Santana, Feira de Santana, Bahia, Brazil

[2]Head and Neck Cancer Division, High Complexity Unit in Oncology of Feira de Santana, Feira de Santana, Bahia, Brazil

[3]Cancer Research Center, Feira de Santana, Bahia, Brazil

Correspondence

Marla S. P. Cruz, Department of Head/Epidemiology and Neck Surgery, Universidade Estadual de Feira de Santana, Transnordestina Avenue, n/n–Novo Horizonte, Feira de Santana–Ba 44036-900, Brazil.
Email: m.smille@hotmail.com

Funding information

Fundação de Amparo à Pesquisa do Estado da Bahia

Abstract

Background: Head and neck cancer (HNC) is a generic term defined on an anatomical–topographic basis to describe malignant tumors located in the oral cavity, pharynx, larynx, and thyroid. A situation commonly presented by individuals with cancer is stress, with evidence indicating a close relationship between stress, behavior, and the immune system with the development and progression of cancer.

Aim: To assess the association between stress levels and quality of life among individuals with HNC.

Methods: This was a cross-sectional study involving 72 HNC patients. The University of Washington Quality of Life Questionnaire was used to assess the quality of life, while the Perceived Stress Scale and salivary cortisol were used to evaluate stress levels.

Results: A negative association was found between quality of life and stress levels as indicated by both the PSS and nighttime salivary cortisol. Nighttime salivary cortisol showed the best accuracy estimated by the area under the receiver operating characteristic curve, slightly better than that of PSS.

Conclusion: Among the time points for saliva sampling, nighttime cortisol was found to have the best accuracy, which was similar to that of the PSS, for the detection of patients with the worst quality of life.

KEYWORDS

cortisol, head and neck neoplasms, oral cancer, psychological stress, quality of life

1 | INTRODUCTION

Head and neck cancer (HNC) is a generic term defined on an anatomical-topographical basis to describe malignant tumors of the upper aerodigestive tract. This anatomical region includes the oral cavity, pharynx, larynx, and thyroid gland.[1]

In Brazil, according to INCA (National Cancer Institute) estimates, 625,000 new cases of cancer are expected in 2020. Among HNCs, oral cancer stands out, with 11,180 new cases, ranking fifth overall in the male population, while larynx cancer, with 6470 new cases, ranks eighth overall among men. In women, 4010 new cases of oral cancer and 1180 new cases of

laryngeal cancer are estimated annually, ranking 12th and 17th, respectively.[2]

Stress is a common issue among cancer patients and is associated with activation of the hypothalamic–pituitary–adrenal (HPA) axis and the main mediators released by the sympathetic nervous system (SNS), namely norepinephrine, epinephrine, adrenocorticotropic hormone (ACTH), and cortisol.[3] Chronic stress affects most physiological systems. Such negative effect results from continued exposure to catecholamines and glucocorticoids, including cortisol.[4]

There is evidence pointing to a close relationship between stress, behavior, the immune system, and cancer development and progression; this stress response to specific stimuli may initiate a chain of events leading up to a variety of adverse health effects.[5–7]

Serum cortisol is a biochemical marker of acute and chronic stress and has been used as such, either alone or together with specific questionnaires in clinical and epidemiological studies.[8]

The experience of cancer by some individuals causes dysregulation of the HPA axis, leading to changes in cortisol circadian rhythm, which may accelerate tumor progression and reduce the quality of life (QOL).[9,10]

As there is a strong relationship between salivary and serum levels of cortisol, salivary measurements have been used in several studies. Easy sampling, noninvasiveness, sample stability at room temperature for up to a week, and high sensitivity make this collection method very appealing.[4,11]

More recent studies have suggested that nighttime cortisol levels may be more appropriate than other collection time points as a marker of stress in women.[12–14] Only one study analyzing QOL and stress levels in HNC patients was found in the literature, which highlights the relevance of the present study.[15] We hypothesized that patients with the greatest stress levels, as determined by subjective perceptions of general stress and objective measures of salivary cortisol, would have the lowest reported QOL. Therefore, the aim of this study was to assess the relationship between stress levels and QOL among HNC patients.

2 | MATERIALS AND METHODS

2.1 | Study design and population

This was a cross-sectional study with 72 patients diagnosed with HNC between February 2017 and July 2019.

We included patients over 18 years of age with a histopathological diagnosis of squamous cell carcinoma or adenocarcinoma whose primary site was the oral cavity, larynx, or pharynx and who were not on corticosteroids, anxiolytics, or antidepressants.

2.2 | Data collection

Before starting data collection, researchers went through a process of orientation and calibration. One of the instruments used in the research was a self-completion questionnaire; however, as most participants had low education levels, researchers sometimes had to apply the questionnaire as an interview. To avoid introducing bias, researchers were told to ask each question up to three times without rephrasing it and, in case of noncomprehension even after the third time, they should replace any difficult word with an easier one without changing the meaning of the question. After such training, researchers were asked to apply the questionnaire to some patients to ensure the correct application.

Data collection took place on the day the patients received the diagnosis, and participants were interviewed individually in a private room. A form was filled out with data obtained directly from patients and their medical records and included the following information: age, sex, race, education, income, alcohol consumption, tobacco use, tumor subsite, and TNM staging (tumor size and extent, metastatic cervical lymph nodes, and presence of distant metastasis) based on the 2010 AJCC/UICC classification (American Joint Committee on Cancer/International Union Against Cancer). Once the T, N, and M are determined, they are then combined to form an overall score. A Roman numeral from I to IV indicates the clinical stage, in which Stage I is the least severe, that is, the tumor is less advanced than that of a stage coming immediately after, and so forth.[16]

The University of Washington Quality of Life Questionnaire (UW-QOL) (version 4) was used for the QOL assessment. This questionnaire consists of 12 questions related to specific head and neck functions as well as activity, recreation, pain, mood, and anxiety, with each question including three to five response categories and a score ranging from zero (worst) to 100 (best); a composite score is also calculated as the mean of the 12 domains.

On the same day, the Perceived Stress Scale (PSS) was administered to subjects to assess how stressful they found everyday life events to be. This scale includes 14 items with response options ranging from zero to four (0 = *never*; 1 = *almost never*; 2 = *sometimes*; 3 = *fairly often*; and 4 = *very often*). The seven positive items (4, 5, 6, 7, 9, 10, and 13) are reversely scored (0 = 4, 1 = 3, 2 = 2, 3 = 1, and 4 = 0), while the remaining items, which are negative, are directly scored, and then the scores are summed across all 14 items, ranging from 0 to 56 points. There is no PSS cutoff point, and the greater the PSS score, the more stressed the respondent is.

Saliva samples for determination of salivary cortisol levels were collected on the day after diagnosis upon awakening, 30 min after awakening, and in the nighttime. Patients were told to collect the nighttime sample between 8 and 10 p.m., before going to sleep. No patient reported working at night. Patients were given three Salivette® saliva collection devices for the day of collection, which allow for easy and clean saliva sampling, and were instructed both verbally and in writing as follows: remove the top cap of the tube, place the cotton swab found inside the Salivette® under the tongue and leave it for 2–3 min or chew it gently for 2–3 min to stimulate saliva flow; do not drink or eat

during collection; after the specified time, return the cotton swab to the Salivette® and immediately close it with the stopper; after collection, keep the Salivette® refrigerated for up to 48 h. The samples were retrieved the day after sampling and were sent to the laboratory for analysis.

An electrochemiluminescence assay was used to measure salivary cortisol levels in nmol/L, and for that, the equipment Modular Analytics E-Module® (Roche Diagnostics) was used.[17]

2.3 | Statistical analysis

Quantitative variables were described by their central tendency (medians) and their respective dispersion measures (interquartile ranges), while nominal variables were described by their absolute values and percentages.

Spearman's correlation coefficient was used to assess the relationship of QOL with the PSS score and salivary cortisol levels, namely cortisol upon awakening, cortisol 30 min after awakening, nighttime cortisol, and mean salivary cortisol levels.

The receiver operating characteristic (ROC) curve was employed to evaluate the diagnostic accuracy of the composite QOL score and stress-related variables (PSS score, cortisol upon awakening, cortisol 30 min after awakening, nighttime cortisol, and mean cortisol levels). For this purpose, QOL scores were divided into quartiles to create four groups, and the first quartile (341–689) was considered the group with the worst QOL. The area under the ROC curve was utilized to estimate test accuracy in predicting cases with the worst QOL.

Ninety-five percent confidence intervals (CIs) were used as a measure of the precision of results. An α level of 0.05 was adopted to indicate statistical significance. MedCalc Statistical Software, version 19.2.3 (MedCalc Software Ltd.), and GraphPad Prism, version 8.0.0 for Windows (GraphPad Software), were used for statistical analysis.

3 | RESULTS

We included 72 patients, with a median age of 62 [55–70] years, of whom 40.3% were married or in a stable union, 36.1% were illiterate, and 76.4% had a monthly income of one minimum wage or less. Additional sociodemographic and clinical characteristics are detailed in Table 1.

The median composite UW-QOL score was 904 [688–1067], while the median PSS score was 24 [18–31]. Median levels of salivary cortisol were 9.8 [6.4–13.5] nmol/L for mean salivary cortisol, 9.3 [5.7–14.0] nmol/L for cortisol upon awakening, 13 [9.8–19.9] nmol/L for cortisol 30 min after awakening, and 2.9 [1.6-5.7] nmol/L for nighttime cortisol.

The correlation of the UW-QOL composite score with the PSS score and salivary cortisol levels is shown in Table 2. We found that the PSS score and nighttime cortisol were negatively associated with the UW-QOL composite score.

The accuracy of nighttime cortisol as estimated by the area under the ROC curve was slightly better than that of the PSS, that is, 75% [95% CI: 62%–82%] and 63% [95% CI: 51%–74%] ($p = 0.284$), respectively (Figure 1).

TABLE 1 Sociodemographic and clinical characteristics of participants with head and neck cancer

Variables	*n*	%
Sex		
Male	55	76.4
Female	17	23.6
Ethnicity		
White	14	19.4
Black	25	34.7
Brown	33	45.8
Smoking		
Smoker or abstinent for <3 years	61	80.2
No	11	19.8
Alcohol consumption		
Drinker or abstinent for <1 year	60	83.3
No	12	16.7
Tumor site		
Mouth	31	43.1
Pharynx	18	25.0
Larynx	23	31.9
Clinical staging		
Stages I and II	21	29.2
Stages III and IV	51	70.8

TABLE 2 Correlations between the University of Washington Quality of Life Questionnaire composite score and both the Perceived Stress Scale score and salivary cortisol variations in the study sample.

Variables	UW-QOL composite score	
	r	*p*
Perceived Stress Scale score	−0.42	<0.001*
Cortisol upon awakening	−0.14	0.210
Cortisol 30 min after awakening	−0.07	0.533
Night-time cortisol	−0.38	0.001*
Mean cortisol	−0.24	0.038*

Abbreviation: *r*, Spearman's correlation.
*$p < 0.05$.

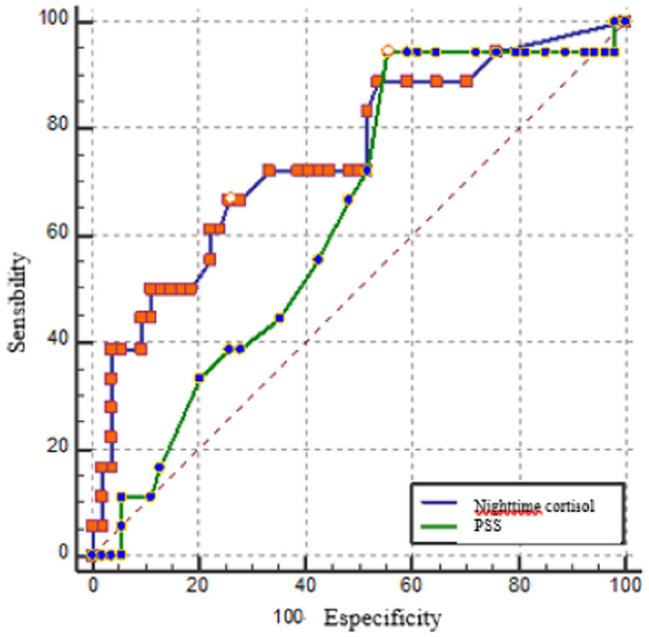

FIGURE 1 Receiver operating characteristic curve assessing the accuracy of the Perceived Stress Scale (PSS) score and nighttime cortisol in detecting cases with the worst quality of life.

4 | DISCUSSION

When an individual is first diagnosed with cancer, they tend to exhibit a psychological response, which may be characterized as chronic stress, anxiety, and depression. Such response will probably manifest in their behavior toward the issue as well as in their physiology.[18] Stress has been reported to be strongly associated with low QOL, mood disorders, and fatigue in patients with breast,[9,19,20] prostate,[21] and lung[22] cancer.

The PSS, which is a self-completion questionnaire, was used in this study to evaluate perceived stress levels. To rely on self-report instruments alone has been demonstrated to lead to an overdiagnosis of stress.[23]

Cortisol, as the main component of the stress response, is responsible for the fight-or-flight behavior and regulates immediate physiological processes such as immune function, which makes it a good indicator for studies assessing stress.[23]

While the consequences of elevated cortisol levels among cancer survivors are largely unknown, cortisol has been linked to mortality and clinical symptoms.[9,24] Changes in cortisol levels may affect the risk of cancer development and progression.[25] However, data on the influence of cortisol levels upon the QOL and prognosis of HNC patients are scarce.

We used two methods for stress assessment in HNC patients (a self-report scale and salivary cortisol levels) and analyzed the relationship between these measures and patient QOL.

One study comparing QOL and stress levels in patients with HNC was found in the literature.[15] Similar studies involving patients with breast, ovarian, prostate, lung, and colorectal cancer have also been published.[9,19,20,22,23,26,27]

In two case–control studies comparing stress levels between HNC patients, patients with premalignant lesions, patients at risk for HNC (tobacco smokers and alcohol drinkers), and healthy controls, a significant increase in salivary cortisol concentrations was found among HNC patients when compared to patients without this diagnosis.[11,23]

In a longitudinal study with 60 HNC patients evaluating anthropometric variables, nutritional status, stress, fatigue, and functional impairment, an increase in the PSS score as well as in serum cortisol levels was observed over time.[15] These data are consistent with our results that HNC patients have increased self-reported and physiological stress levels.

Published HNC studies comparing salivary cortisol levels between groups or over time were either case–control or longitudinal studies. This, however, was a cross-sectional study aiming to find an association between worse QOL and increased stress levels, as indicated by both perceived stress and salivary cortisol. Although a moderate association, we found an association between the UW-QOL composite score and both the PSS score and salivary cortisol levels, specifically nighttime cortisol and mean salivary cortisol.

Our findings regarding perceived stress are in line with those reported by Fong and Ho[28] for patients with colorectal cancer, by Ravidran et al.[29] for cancer patients and survivors, and by Karvinen et al.[30] for lung cancer survivors.

As for nighttime cortisol, similar findings were reported in a study with women diagnosed with ovarian cancer, in which nighttime cortisol levels were positively correlated with fatigue and negatively associated with clinical condition and performance status.[13] In a separate publication, elevated nighttime cortisol levels were reported to be associated with worse survival rates in patients with ovarian cancer.[31]

Others have also reported statistically significant associations between changes in cortisol levels and low QOL, showing patients diagnosed with ovarian[32] and breast[10,33] cancer with high cortisol levels had poor QOL.

We found nighttime cortisol and the PSS score to have accuracies of 75% and 63%, respectively, in detecting low QOL, and so cortisol was found to be a better indicator of poor QOL in our analysis.

In a study assessing nighttime cortisol as an isolated marker of stress in breast cancer patients, an association between nighttime cortisol, but not daytime cortisol, and a flattened diurnal cortisol slope was found, suggesting that high nighttime cortisol concentrations were responsible for a flattened diurnal cortisol slope.[12] These findings corroborate our report of a negative correlation between nighttime salivary cortisol levels and QOL in HNC patients.

Our results suggest that nighttime cortisol may be a robust measure of stress in patients with HNC when compared to the PSS, as our population had low education levels and thus had difficulty completing the PSS questions. Nighttime cortisol may therefore be a more precise instrument since it is a biological marker.

Our study has some limitations. First, saliva sampling took place on a single day, and so cortisol levels might have been influenced by unrelated stressful events that occurred at the time. Second, our cross-sectional design renders our findings correlational, precluding causal inferences about salivary cortisol levels and worsening QOL. Third, this was a single-center study with a homogeneous population in relation to socioeconomic characteristics. In addition, the instrument we used to assess stress evaluates general stress and not cancer-specific stress.

The results found are important, as they reveal that psychological issues and stress are associated with a low QOL in individuals with HNC. Thus, monitoring these issues should be considered, from diagnosis to posttreatment in patients with HNC, which is necessary for a better QOL in these individuals and an increase in survival rates.

Our findings should, therefore, encourage longitudinal studies to elucidate the ways in which psychological and physiological changes, such as changes in the circadian clock, specifically in nighttime cortisol, might be associated with QOL in patients with HNC over time.

5 | CONCLUSION

A negative correlation between QOL and stress levels, as indicated by salivary cortisol concentrations and the PSS score, was found in this study. Nighttime cortisol was shown to have the best diagnostic accuracy in identifying HNC patients with the worst QOL.

AUTHOR CONTRIBUTIONS

Marla S. P. Cruz: Conceptualization; data curation; funding acquisition; investigation; methodology; writing—original draft. **Tercio G. Reis**: Conceptualization; resources; supervision. **Antoniel C. Oliveira**: Investigation; writing—original draft. **Marluce M. Macedo**: Investigation. **José de Bessa**: Methodology; validation; visualization; writing—review and editing. **Márcio C. Oliveira**: Conceptualization; funding acquisition; resources; supervision; writing—review and editing.

ACKNOWLEDGMENT

This study was supported by Fundação de Amparo à Pesquisa do Estado da Bahia (FAPESB). The authors would like to thank the staff of Núcleo de Pesquisa em Câncer de Cabeça e Pescoço who have helped us during the research. We would also like to thank the High Complexity Oncology Unit of Santa Casa de Miser-icórdia de Feira de Santana, Dom Pedro de Alcântara Hospital, and MULTICLIN clinic who provided us the location for our research.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. All authors have read and approved the final version of the manuscript, have full access to all of the data in this study, and take complete responsibility for the integrity of the data and the accuracy of the data analysis.

ETHICS STATEMENT

This study was independently reviewed and approved by the State University of Feira de Santana Research Ethics Committee under protocol no. 1.621.470. All subjects voluntarily agreed to participate in this study and provided written informed consent in full accordance with ethical principles.

TRANSPARENCY STATEMENT

Marla S. P. Cruz affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

ORCID

Marla S. P. Cruz http://orcid.org/0000-0002-2698-5480
Tercio G. Reis http://orcid.org/0000-0002-6147-6307

REFERENCES

1. Dobrossy L. Epidemiology of head and neck cancer: magnitude of the problem. *Cancer Metastasis Rev*. 2005;24:9-17.
2. INCA. Coordenação de Prevenção e Vigilância. Estimativa 2020: incidência de câncer no Brasil/Instituto Nacional de Câncer José Alencar Gomes da Silva. Coordenação de Prevenção e Vigilância. INCA; 2019. Accessed June 21, 2020. https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//estimativa-2020-incidencia-de-cancer-no-brasil.pdf
3. Fang CY, Reibel DK, Longacre ML, Rosenzweig S, Campbell DE, Douglas SD. Enhanced psychosocial well-being following participation in a mindfulness-based stress reduction program is associated with increased natural killer cell activity. *J Altern Complement Med*. 2010;16(5):531-538.
4. McEwen BS. Sex, stress and the hippocampus: allostasis, allostatic load and the aging process. *Neurobiol Aging*. 2002;23(5):921-939.
5. Chandwani KD, Ryan JL, Peppone LJ, et al. Cancer-related stress and complementary and alternative medicine: a review. *Evid Based Complement Alternat Med*. 2012;2:979213-979215.
6. Lucas VS, McCain N, Elswick RK, Pozez AL. Perceived stress and surgical wound cytokine patterns. *Plast Surg Nurs*. 2018;38(2):55-72.
7. Denaro N, Tomasello L, Russi EG. Cancer and stress: what's matter? from epidemiology: the psychologist and oncologist point of view. *J Cancer Ther Res*. 2014;3:6.
8. Chaby LE, Cavigelli SA, Hirrlinger AM, Caruso MJ, Braithwaite VA. Chronic unpredictable stress during adolescence causes long-term anxiety. *Behav Brain Res*. 2015;278:492-495.
9. Abercrombie HC, Giese-Davis J, Sephton S, Epel ES, Turner-Cobb JM, Spiegel D. Flattened cortisol rhythms in metastatic breast cancer patients. *Psychoneuroendocrinology*. 2004;29(8):1082-1092.
10. Cash E, Sephton SE, Chagpar AB, et al. Circadian disruption and biomarkers of tumor progression in breast cancer patients awaiting surgery. *Brain Behav Immun*. 2015;48:102-114.
11. Bernabé DG, Tamae AC, Miyahara GI, Sundefeld ML, Oliveira SP, Biasoli ÉR. Increased plasma and salivary cortisol levels in patients with oral cancer and their association with clinical stage. *J Clin Pathol*. 2012;65(10):934-939.

12. Allende S, Medina JL, Spiegel D, Zeitzer JM. Evening salivary cortisol as a single stress marker in women with metastatic breast cancer. *Psychoneuroendocrinology*. 2020;115:104648.
13. Weinrib AZ, Sephton SE, Degeest K, et al. Diurnal cortisol dysregulation, functional disability, and depression in women with ovarian cancer. *Cancer*. 2010;116(18):4410-4419.
14. Schrepf A, Clevenger L, Christensen D, et al. Cortisol and inflammatory processes in ovarian cancer patients following primary treatment: relationships with depression, fatigue, and disability. *Brain Behav Immun*. 2013;30 Suppl:S126-S134. doi:10.1016/j.bbi.2012.07.022
15. Silver HJ, de Campos Graf Guimaraes C, Pedruzzi P, et al. Predictors of functional decline in locally advanced head and neck cancer patients from south Brazil. *Head Neck*. 2010;32(9):1217-1225.
16. American Joint Committee on Cancer. *AJCC Cancer Staging Manual*. Springer; 2010.
17. Gagnon N, Frechette I, Mallet PL, Dube J, Houde G, Fink GD. Establishment of reference intervals for the salivary cortisol circadian cycle, by electrochemiluminescence (ECLIA), in healthy adults. *Clin Biochem*. 2018;54:56-60.
18. Dedert E, Lush E, Chagpar A, et al. Stress, coping, and circadian disruption among women awaiting breast cancer surgery. *Ann Behav Med*. 2012;44(1):10-20.
19. Carlson LE, Speca M, Patel KD, Goodey E. Mindfulness-based stress reduction in relations to quality of life, mood, symptoms and stress and immune parameters in breast and prostate cancer outpatients. *Psychosom Med*. 2003;65:571-581.
20. Carlson LE, Speca M, Patel KD, Goodey E. Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress and levels of cortisol, dehydroepiandrosterone-sulftate (DHEAS) and melatonin in breast and prostate cancer outpatients. *Psychoneuroendocrinology*. 2004;29:448-474.
21. Sharpley CF, Christie DRH, Bitsika V, et al. Limitations in the inverse association between psychological resilience and depression in prostate cancer patients experiencing chronic physiological stress. *Psychooncology*. 2018;27(1):223-228.
22. Chang WP, Lin CC. Relationships of salivary cortisol and melatonin rhythms to sleep quality, emotion, and fatigue levels in patients with newly diagnosed lung cancer. *Eur J Oncol Nurs*. 2017;29:79-84.
23. Sharma P, Sandhu SV, Bhandari R, Verma I, Bhullar RK, Khangura RK. Estimation of cortisol levels in patients with premalignant disorders and oral squamous cell carcinoma. *J Oral Maxillofac Pathol*. 2018;22(1):27-34.
24. Sephton SE, Sapolsky RM, Kraemer HC, Spiegel D. Diurnal cortisol rhythm as a predictor of breast cancer survival. *J Natl Cancer Inst*. 2000;92(12):994-1000.
25. Spiegel D. Mind matters in cancer survival. *JAMA*. 2011;305(5):502-503.
26. Mormont MC, Waterhouse J, Bleuzen P, et al. Marked 24-h rest/activity rhythms are associated with better quality of life, better response, and longer survival in patients with metastatic colorectal cancer and good performance status. *Clin Cancer Res*. 2000;6(8):3038-3045.
27. Lengacher CA, Reich RR, Paterson CL, et al. A large randomized trial: effects of mindfulness-based stress reduction (MBSR) for breast cancer (BC) survivors on salivary cortisol and IL-6. *Biol Res Nurs*. 2019;21:49-59.
28. Fong TCT, Ho TH. Mindfulness facets predict quality of life and sleep disturbance via physical and emotional distresses in Chinese cancer patients: a moderated mediation analysis. *Psycho-Oncology*. 2020;29:894-901.
29. Ravidran OS, Shankar A, Murthy T. Comparative study on perceived stress, coping, quality of life, and hopelessness between cancer patients and survivors. *Indian J Palliat Care*. 2019;25(3):414-420.
30. Karvinen KH, Murray NP, Arastu H, Allison RR. Stress reactivity, health behaviors, and compliance to medical care in breast cancer survivors. *Oncol Nurs Forum*. 2013;40(2):149-156.
31. Schrepf A, Thaker PH, Goodheart MJ, et al. Diurnal cortisol and survival in epithelial ovarian cancer. *Psychoneuroendocrinology*. 2015;53:256-267.
32. Armer JS, Clevenger L, Davis LZ, et al. Life stress as a risk factor for sustained anxiety and cortisol dysregulation during the first year of survivorship in ovarian cancer. *Cancer*. 2018;124(16):3401-3408.
33. Rebholz WN, Cash E, Zimmaro LA, et al. Distress and quality of life in an ethnically diverse sample awaiting breast cancer surgery. *J Health Psychol*. 2018;23(11):1438-1451.

How to cite this article: Cruz MSP, Reis TG, Oliveira AC, Macedo MM, de Bessa J, Oliveira MC. Nighttime salivary cortisol as a biomarker of stress and an indicator of worsening quality of life in patients with head and neck cancer: a cross-sectional study. *Health Sci Rep*. 2022;5:e783. doi:10.1002/hsr2.783