Contents lists available at ScienceDirect

Comprehensive Psychoneuroendocrinology

Predisposing factors for increased cortisol levels in oral cancer patients

Jéssica Araújo Figueira [a], Bruna Amélia Moreira Sarafim-Silva [a], Gislene Maria Gonçalves [a], Laerte Nivaldo Aranha [b], Flávia Lombardi Lopes [c], José Eduardo Corrente [d], Éder Ricardo Biasoli [a], Glauco Issamu Miyahara [a], Daniel Galera Bernabé [a,*]

[a] *Psychosomatic Research Center, Oral Oncology Center, São Paulo State University (UNESP), School of Dentistry, Araçatuba, São Paulo, 15050-015, Brazil*
[b] *Sabin Laboratory, Birigui, São Paulo, 16200-001, Brazil*
[c] *Department of Production and Animal Health, São Paulo State University (UNESP), School of Veterinary Medicine, Araçatuba, São Paulo, 16050-680, Brazil*
[d] *Research Support Office, Botucatu Medical School (UNESP), Botucatu, São Paulo, 18618-687, Brazil*

ARTICLE INFO

ABSTRACT

Cancer patients may have a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and abnormal secretion of cortisol. Increased cortisol levels have been associated with worse prognosis in patients with different types of tumors. Although anxiety and depression can trigger an abnormal cortisol secretion, little is known regarding the influence of these emotional disorders on HPA axis dysregulation in cancer patients when evaluating together with demographic, clinicopathological and biobehavioral variables. This cross-sectional study analyzed the pre-treatment plasma cortisol levels of 133 patients with oral squamous cell carcinoma (OSCC) and its association with demographic, clinicopathological, biobehavioral and psychological variables. Plasma cortisol levels were measured by electrochemiluminescence, and anxiety and depression symptoms were assessed using Beck Anxiety Inventory (BAI) and Depression (BDI), respectively. Demographic, clinicopathological and biobehavioral data were collected from patients' medical records. Results from multivariate analysis showed that the occurrence of cancer-induced pain was predictive for higher cortisol levels (OR = 5.388, p = 0.003). Men with OSCC were 4.5 times more likely to have higher plasma cortisol levels than women (OR = 4.472, p = 0.018). The effect of sex on cortisol concentrations was lost in the adjusted model for clinical staging (OR = 2.945, p = 0.116). The absence of chronic alcohol consumption history was a protective factor for highest hormone concentrations in oral cancer patients (OR = 0.104, p = 0.004). Anxiety symptoms measured by BAI as "hands trembling" (OR = 0.192, p = 0.016) and being "nervous" (OR = 0.207, p = 0.0004) were associated with lower cortisol levels. In contrast, the feeling of "fear of losing control" was a risk factor for highest hormone concentrations (OR = 6.508, p = 0.0004). The global score and specific symptoms of depression measured by the BDI were not predictive for plasma hormone levels (p > 0.05). Together, our results show that pain, alcohol consumption and feeling fear are independent factors for increased systemic cortisol levels in patients with oral cancer. Therefore, psychological intervention, as well as control of pain and alcohol consumption, should be considered to prevent the negative effects of cortisol secretion dysregulation in cancer patients.

1. Introduction

Cancer onset and progression may be affected by psychoneuroimmunological factors [1,2]. Stress, anxiety and depression result in neurohormonal dysregulation affecting the immune system and cancer progression [1,3,4]. The neuroendocrine and immune systems share common mediators and receptors signals, suggesting that the brain plays an immunoregulatory role [5]. Psychological processes activate the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis, promoting increased secretion of stress-related neurohormonal mediators, such as catecholamines and cortisol [4]. It has been shown that cortisol plays a role in tumorigenesis and cancer progression [4,6,7]. The hormone may promote DNA damage and interfere on DNA repair, an event eminently mediated by glucocorticoid receptors [6,8,9]. In a pre-clinical model of chronic stress, Feng et al. observed increased tumorigenesis and attenuation of

---

p53 function which could be mediated by elevated glucocorticoids levels [10].

Abnormal plasma cortisol levels have been associated with shorter disease-free interval in ovarian and breast cancer patients [11,12]. In addition, a stimulatory effect of cortisol on cell proliferation has been observed in different cancer cell lines [13,14]. In general, cancer patients experience high levels of stress, anxiety and depression during different phases of treatment [15]. Association between cortisol levels and psychological symptoms has been demonstrated in healthy and oncological patients [16,17]. In a recent study, high systemic cortisol levels were associated with depression and occurrence of anxiety symptoms in healthy patients [17]. Newly diagnosed lung cancer patients, for example, share both higher levels of depression and higher salivary cortisol levels compared to healthy adults [18].

Head and neck cancer (HNC) comprises malignancies of the upper aero digestive tract as oral cavity, oropharynx, pharynx and larynx, and is the seventh most common type of cancer in the world [19]. Among HNCs, oral squamous cell carcinomas (OSCC) are the most frequent tumors, with chronic tobacco and alcohol consumption being the main risk factors [20]. Despite advances in cancer diagnosis and treatment, the 5-year survival rate is only 50% for patients with OSCC [21]. In previous studies, we showed that patients with OSCC have higher systemic levels of catecholamines and cortisol compared to non-cancer patients [22,23]. Increased cortisol levels have been associated with advanced stage of oral cancer [22]. Patients with HNC, including OSCC, also experience a high rate of emotional disorders such as depression and anxiety [24]. Increased anxiety and depression levels in HNC patients have been linked with regional lymph node metastases, shorter survival, and worse quality of life [16,25,26].

Despite the evidence of emotional disorders and dysregulation of cortisol secretion, no study has focused on the interaction of these phenomena in HNC patients. Furthermore, little is known regarding the independent predictors for HPA axis dysregulation in patients with cancer, when clinicopathological, biobehavioral and psychological variables are analyzed together. In the current study we analyzed for the first time the association of plasma cortisol levels with clinicopathological, biobehavioral and psychological variables in patients with oral cancer.

2. Patients and methods

2.1. Ethics statement

This study was approved by the Committee of Human Studies of the Sao Paulo State University (UNESP), School of Dentistry, Araçatuba, São Paulo, Brazil (nº. 35314720.9.0000.5420) and informed consent was obtained from all participants.

2.2. Patients

The patients with oral cancer were recruited from the Oral Oncology Center, Sao Paulo State University (UNESP), School of Dentistry, Araçatuba, São Paulo, Brazil. Inclusion criteria were patients over 18 years of age; with histopathological diagnosis of OSCC; and primary tumor located in the anterior two-thirds of the tongue, floor of the mouth, retromolar area, buccal mucosa, gingiva, or hard palate. Exclusion criteria were previous history of cancer; any previous oncological treatment; or inability to perform blood collection or psychological tests.

2.3. Demographic, Clinicopathological and biobehavioral variables

Demographic, Clinicopathological and biobehavioral data were extracted from patients' clinical records. Demographic variables (age, sex, marital status, living with someone, education and family income), clinicopathological variables (comorbidity, pain related to the primary tumor, clinical staging, primary tumor size (T), presence of regional

metastases (N) and tumor histological grade) and biobehavioral data (sleep quality, history and intensity of tobacco and alcohol consumption) were obtained in OSCC patients' admission and before treatment decision. Comorbidities were assessed according to the Charlson Comorbidity Index (CCI) [27]. Clinical staging was defined according to the Union for International Cancer Control (UICC) [28]. Visual Analog Scale were used to estimate primary tumor-related pain intensity at the time of data collection and classified in a scale from 0 (absence of pain) to 10 (severe pain). The patient' self-reports of sleep quality in the previous night was classified as very good, good, regular, bad and terrible [23,29]. Tobacco and alcohol consumption intensity was assessed using a score scale of 1–4 points according to the amount of cigarette or doses of alcohol consumed per day: non-smoker/drinker, light use (1–10 cigarettes/1–2 drinks per day), moderate use (11–20 cigarettes/3–4 drinks per day), and heavy use (more than 20 cigarettes/more than 4 drinks per day) [29].

2.4. Anxiety and depression symptoms

Anxiety and depression symptoms were assessed by interviews using the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI), respectively [29–31]. The tests were applied by a psychologist on the same day of blood samples collection. BAI and BDI are a self-report inventory with 21 items which evaluate the frequency of anxiety and depression symptoms that occurred in the last week [30,31]. In both scales, the self-report severity of each anxiety or depression symptoms ranged from 0 (absolutely not/none); 1 (mild); 2 (moderate) to 3 (severe). The overall BAI and BDI scores were graded in four levels, respectively: minimal (0–10; 0–11), mild (11–19; 12–19), moderate (20–30; 20–35) and severe (31–63; 36–63) levels.

2.5. Blood samples

Blood samples were collected from oral cancer patients before oncological treatment and on the same day as the psychological evaluation. All blood collections were performed with patients fasting between 8:00 a.m. and 10:00 a.m. to avoid diurnal variations. To prevent clotting, samples of peripheral blood were collected with a syringe treated with EDTA. After collection, blood samples were immediately centrifuged at 1500 rpm under refrigeration at 4°C for 20 min and plasma was stored at −80°C.

2.6. Measurement of plasma cortisol

Plasma cortisol levels were measured by electrochemiluminescence immune assay method using the Elecsys Cortisol II reagent kit (Roche Diagnostics GmbH, Mannheim, Germany) in a Cobas E411 auto analyzer (Roche Diagnostics GmbH, Mannheim, Germany). This assay is based on the competition test principle, using a specific monoclonal antibody against cortisol and a ruthenium-labeled analogue [32]. The chemiluminescent reaction was induced by applying a voltage to the electrode and measured by a photomultiplier [32]. The assay was performed according to the manufacturer's instructions. The detection limit of the assay was 1.5 nmol/L and measuring range was 1.5–1750 nmol/L. The coefficients of variation inter-assay and intra-assay were ≤5% and ≤6%, respectively.

2.7. Statistical analysis

Statistical analyses were performed using the SAS software (version 9.4; SAS Institute, Inc, Cary, North Carolina). Chi-square and Fisher's exact tests were used to evaluate the association between cortisol plasma levels and demographic, clinicopathological or biobehavioral variables, as well as the anxiety and depression symptoms. Multivariate regression analysis was performed by the stepwise logistic regression method, considering the plasma cortisol levels as a dependent variable, and the

demographic, clinicopathological, biobehavioral and psychological characteristics as explanatory variables. Logistic regression was performed considering two different models according to the categorization of plasma cortisol levels. In model 1 scores below and above the median were used to define patients with lower and higher plasma cortisol levels, respectively. In model 2 cortisol concentrations were categorized by quartile in very high, high, low and very low plasma cortisol levels. Each model was adjusted for potential confounders. The median was also used as cutoff point for BAI and BDI scores. Each anxiety and depression symptom reported in BAI and BDI, respectively, was also analyzed separately by two different measures: binary measure according to symptom occurrence (yes or no) and severity categories (0, none; 1, mild; 2, moderate; or 3, severe). Significance level was set at 5% (p < 0.05) for all analyses.

3. Results

3.1. Epidemiological and clinicopathological profile

One hundred and thirty-three patients with OSCC met the inclusion criteria. Their demographic and clinicopathological characteristics are showed in Table 1. Most of the patients were men (78.8%), middle aged (63.2%) and married (51.1%). The minority lived alone (12.4%), whereas 87.6% live with a partner or relative. Most patients had completed elementary school (48.2%), and family income of R $1000–5000 (1 USD = 5 Reais, approximately) per month (45.7%). Regarding clinicopathological data, tongue (39.8%) and floor of the mouth (27.1%) were the most common sites of OSCC. Most OSCC patients had the disease classified in advanced stage (III and IV) (51.8%), and tumors microscopically graded in moderately differentiated (66.0%). Forty-three percent of the patients reported pain related to the primary tumor. Most of them had moderate pain (23.7%), followed by 12.4% with minimum pain and 7.2% with intense pain. Sixty-one patients displayed at least one comorbidity (45.9%) (Table 1).

3.2. Biobehavioral and psychological characteristics

The biobehavioral and psychological variables of the OSCC patients are described in Table 2. Most patients were smokers (73.7%). In relation to tobacco consumption intensity, 29.3% of them reported light, 30.1% moderate and 26.3% heavy tobacco consumption. The majority of patients were drinkers (55.6%) with a history of heavy alcohol intake (36.8%). For almost half of the patients the quality of sleep in the previous night was good, while 17.5% classified the sleep as very good and 23.8% as regular. Only eight patients (8.2%) reported have had a bad or terrible sleep. Regarding psychological characteristics, most of OSCC patients displayed minimum levels of anxiety (68.8%) and depression (67.9%) symptoms, followed by mild (20.4%, BAI; 21.4%, BDI), moderate (8.6%, BAI; 9.5%, BDI) and severe (2.1%, BAI; 1.2%, BDI) (Table 2).

3.3. Associations between plasma cortisol levels and demographic, clinicopathological, biobehavioral and psychological variables

In the univariate analysis considering cortisol concentrations stratified into two levels, male patients displayed higher levels of plasma cortisol compared to females (p = 0.005) (Table 3). When the associations between clinicopathological variables and systemic cortisol levels were analyzed, OSCC patients who had regional metastasis showed increased hormone levels than patients without regional metastasis (p = 0.030). The presence and intensity of pain related to primary tumor were associated with higher plasma cortisol levels. OSCC patients who had pain, regardless of its intensity, showed higher levels of systemic cortisol than patients without pain (p = 0.003). Also, patients who had intense pain displayed higher plasma cortisol concentrations in comparison to patients with moderate and minimum intensity or no pain (p

Table 1
Demographic and clinicopathological profile of OSCC patients.

Variable	Nº (%)
Sex	
Male	105 (78.9)
Female	28 (21.1)
Age	
0–45 y	18 (13.5)
46–65 y	84 (63.2)
>65 y	31 (23.3)
Marital status	
Single	31 (23.3)
Married	68 (51.1)
Divorced	18 (13.5)
Widowed	16 (12.0)
Living alone*	
No	71 (87.6)
Yes	10 (12.4)
Education*	
Illiterate	4 (4.9)
Incomplete primary school	19 (23.5)
Elementary school	39 (48.2)
High school	15 (18.5)
University	4 (4.9)
Family income*	
R$0/mo	5 (6.1)
<R$1000/mo	23 (28.4)
R$1000–5000/mo	37 (45.7)
>R$5000/mo	16 (19.8)
T classification	
T1	32 (24.1)
T2	35 (26.3)
T3	28 (21.1)
T4	38 (28.6)
Regional metastasis	
N0	93 (69.9)
N+	40 (30.1)
Clinical stage	
I	32 (24.1)
II	32 (24.1)
III	18 (13.5)
IV	51 (38.3)
Histopathologic grade*	
In situ	5 (4.7)
Well-differentiated	25 (23.6)
Moderately-differentiates	70 (66.0)
Poorly-differentiated	6 (5.7)
Comorbidity	
No	72 (54.1)
Yes	61 (45.9)
CCI score	
0	72 (54.1)
1	43 (32.3)
2	14 (10.5)
3	4 (3.0)
Pain intensity*	
No	55 (56.7)
Minimum	12 (12.4)
Moderate	23 (23.7)
Intense	7 (7.2)

Abbreviation: CCI, Charlson Comorbidity Index.
*Variables with missing data.

= 0.015). Regarding the biobehavioral variables, both alcohol consumption and intensity were positively associated with hormone levels. Drinker OSSC patients had higher levels of plasma cortisol than non-drinker or ex-drinker patients (p = 0.005). High alcohol consumption was also associated with increased hormone levels (p = 0.015). In the univariate analysis, global anxiety scores were not associated to plasma cortisol levels. However, significant associations were observed between systemic hormone levels and specific anxiety symptoms measured by the BAI. Cancer patients who reported occurrence of "dizzy or lightheaded" (p = 0.038), "heart pounding/racing" (p = 0.02) and "hands trembling" (p = 0.03) had lower levels of plasma cortisol compared to patients without these symptoms. Severe intensity of the symptoms "heart

Table 2

Biobehavioral and psychological characteristics of OSCC patients.

Variable	Nº (%)
Smoking	
Non-smoker	19 (14.3)
Current smoker	98 (73.7)
Ex-smoker	16 (12.0)
Tobacco intensity	
Non-smoker	19 (14.3)
Light	39 (29.3)
Moderate	40 (30.1)
Heavy	35 (26.3)
Alcohol consumption	
Non-drinker	25 (18.8)
Current drinker	74 (55.6)
Ex-drinker	34 (25,6)
Alcohol intensity	
Non-drinker	25 (18.8)
Light	36 (27.1)
Moderate	23 (17.3)
Heavy	49 (36.8)
Sleep quality (previous night)*	
Very good	17 (17.5)
Good	49 (50.5)
Regular	23 (23.8)
Bad	4 (4.1)
Terrible	4 (4.1)
BAI*	
Minimum	64 (68.8)
Mild	19 (20.4)
Moderate	8 (8.6)
Severe	2 (2.1)
BDI*	
Minimum	57 (67.9)
Mild	18 (21.4)
Moderate	8 (9.5)
Severe	4 (1.2)

Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory.
*Variables with missing data.

Table 3

Significant associations between demographic, clinicopathological, biobehavioral and psychological variables and plasma cortisol levels in OSSC patients.

Variable[a]	Median (*P-value*)	Quartile (*P-value*)
Sex (male)	.004	.047
Education (elementary school)	–	.031
Regional metastasis (N)	.030[b]	–
Pain	.002[b]	.022[b]
Pain intensity (intense)	.015[c]	–
Smoking	–	.018[d]
Alcohol consumption (current drinker)	.005[d]	.025[d]
Alcohol intensity (heavy intensity)	.015[e]	–
Anxiety symptoms (BAI)		
"dizzy or lightheaded"	.038[b]	–
"heart pounding/racing"	.018[b]	–
"heart pounding/racing" intensity	.033[c]	–
"hands trembling"	.026[b]	–
"scared"	.046[f]	–
"fear of losing control"	–	.022[b]
Depression symptoms (BDI)		
Depression symptom (yes vs no)	–	.000[b]
"suicide ideation"	–	.047[b]

[a] The variables' associations with plasma cortisol levels reached statistical significance.
[b] Values were measured with the binary measure (yes or no).
[c] Values were measured with the severity categories (none, mild, moderate, or intense).
[d] Non-smoker/drinker, current smoker/drinker, or ex-smoker/drinker.
[e] Light, moderate, or heavy.
[f] Little (none and mild), or very (moderate and intense).

pounding/racing" (p = 0.03) and of being "scared" (p = 0.04) were also associated to lower plasma cortisol levels (Table 3). When quartile categorization was used to stratify cortisol concentrations, highest hormone levels were associated with male sex, mid education (elementary school), smoking, alcoholism and pain related to the tumor. Regarding psychological factors, highest levels of plasma cortisol were also associated with BAI symptom of "fear of losing control", presence of one or more depression symptoms, and the specific BDI symptom of "suicide ideation" (Table 3).

3.4. Independent predictive factors for plasma cortisol levels

To identify which variables are predictive of diurnal cortisol secretion in oral cancer patients, logistic regression analyses were performed considering cortisol concentrations stratified into two levels (model 1) and quartiles (model 2). The models were also adjusted for possible confounders, such as demographic variables (age, marital status, and familiar income), smoking, drinking and clinical staging, considered as possible confounders. Multivariate analysis using model 1 showed that male OSCC patients were 4.5 times more likely to display higher plasma cortisol levels (OR = 4.472, 95% CI = 1.282–15.596, p = 0.018). However, when the model was adjusted for clinical staging, no significant association between sex and plasma cortisol levels was found (OR = 2.945, 95% CI = 0.764–11.354, p = 0.116) (Table 4). OSCC patients who reported pain related to primary tumor displayed 5.3 times more chances of have increased levels of plasma cortisol (OR = 5.388, 95% CI = 1.75–16.587, p = 0.003). This result was kept even in the adjusted model (OR = 4.821, 95% CI = 1.514–15.359, p = 0.007). One BAI symptom was considered a protection factor to increased cortisol levels in patients with oral cancer. Patients who self-reported "hands trembling" had 81% less chance of having increased hormone levels than patients who did not have this symptom (OR = 0.192, 95% CI = 0.05–0.741, p = 0.016). This significant association was also found when the model was adjusted for clinical staging (OR = 0.163, 95% CI = 0.038–0.706, p = 0.015) (Table 4). When cortisol concentrations were stratified in quartiles (model 2) the occurrence of pain related to primary tumor remained as a risk factor for the highest levels of cortisol in OSCC patients (OR = 2.634, 95% CI = 1.135–6.113, p = 0.024), but not in the adjusted model for family income (OR = 1.887, 95% CI = 0.702–5.075, p = 0.208). Using model 2 in logistic regression, alcohol abstinence was a protection factor against elevated cortisol levels. OSCC patients who were non-drinkers had 90% less chance of displaying very high cortisol levels than drinkers (OR = 0.104, 95% CI = 0.03–0.353, p = 0.004). This significant effect of alcohol consumption status on high cortisol levels remained even after the model was adjusted for possible confounding variables (OR = 0.187, 95% CI = 0.042–0.827, p = 0.035). Regarding psychological evaluation, two anxiety symptoms were predictive for systemic cortisol levels in the multivariate analysis using model 2. OSCC patients who reported being nervous had lower chances of having very high plasma cortisol levels (unadjusted model, OR = 0.207, 95% CI = 0.087–0.497, p = 0.0004; adjusted model, OR = 0.272, 95% CI = 0.102–0.724, p = 0.009). In contrast, the symptom "fear of losing control" was considered a risk factor for the highest concentrations of cortisol. OSCC patients who reported being afraid of losing control had a 6.5-fold and 4.3-fold increase in the chance of displaying very high plasma cortisol levels in the unadjusted (OR = 6.508, 95% CI = 2.328–18.194, p = 0.0004) and adjusted model (OR = 4.315, 95% CI = 1.31–14.21, p = 0.016), respectively (Table 4). Our results showed that both global depression levels and the BDI subscales were not predictive for the plasma cortisol levels in OSCC patients, regardless of the logistic regression model used.

4. Discussion

In the last few decades, there has been a growing body of evidence showing the role of cortisol dysregulation in immune system impairment

Table 4

Significant results from stepwise logistic regression analyses considering plasma cortisol levels as response variable and demographic, clinicopathological, biobehavioral and psychological data from OSCC patients as independent variables.

Independent Variables	Dependent Variable: Plasma Cortisol Levels											
	Model 1[a]						Model 2[b]					
	OR no ajustment	95% CI	P value	OR ajusted[d]	95% CI	P value	OR no ajustment	95% CI	P value	OR ajusted[d]	95% CI	P value
Sex (male vs female)	4.472	1.282–15.596	0.018	2.945	0.764–11.354	0.116	–	–	–	–	–	–
Painc	5.388	1.75–16.587	0.003	4.821	1.514–15.359	0.007	2.639	1.135–6.113	0.024	1.887	0,792–5.075	0.208
Alcohol consumption (non-drinker vs drinker)[c]	–	–	–	–	–	–	0.104	0.03–0.353	0.004	0.187	0.042–0.827	0.035
Anxiety symptoms (BAI)												
"hands trembling"c	0.192	0.05–0.741	0.016	0.163	0.038–0.706	0.015	–	–	–	–	–	–
"nervous"c	–	–	–	–	–	–	0.207	0.087–0.497	0.0004	0.272	0.102–0.724	0.0007
"fear of losing control"c	–	–	–	–	–	–	6.508	2.328–18.194	0.0004	4.315	1.31–14.21	0.016

[a] Considering model 1 (cortisol levels categorized into two categories).
[b] Considering model 2 (cortisol levels categorized into four categories).
[c] Values were measured with the binary measure (yes or no).
[d] Models adjusted for age, marital status, family income, and clinical staging.

and cancer progression. In the current study, we investigated the predictive factors for systemic cortisol levels in oral cancer patients exploring demographic, clinicopathological, biobehavioral and psychological variables. The results revealed that pain, alcohol consumption and anxiety symptoms are independent predictors of diurnal cortisol levels in cancer patients. Multivariate analysis showed that pain related to the primary tumor was associated with increased plasma cortisol levels. Oral cancer patients with pain had a 5.3-fold increase in the chance of having higher plasma cortisol levels. The occurrence of pain was also a risk factor for the highest hormone concentrations categorized by quartile, but this effect was lost when the model was adjusted for familiar income. The activation of HPA axis induced by stress and subsequently cortisol disfunction are linked to pain and inflammation [33,34]. Anxiety has also been identified as a significant predictor of pain [35,36]. Pain itself can be a stressor, and maladaptive response to pain may intensify the symptom [37]. In patients with advanced cancer, [38] also observed a significant association between elevated serum cortisol concentrations and high levels of pain. Our results demonstrated not only the association of elevated tumor-induced pain and cortisol diurnal secretion, but also the presence of pain as an independent variable for increased systemic cortisol levels. These findings indicate the importance of an effective pain control in cancer not only for a better patient's quality of life, but also to prevent detrimental effects of neurohormonal dysregulation.

Our results also showed that male patients with OSCC had 4.4 times more chances to have increased plasma cortisol levels when compared to female patients. However, this effect was lost when the regression model was adjusted for clinical staging. Although this was not a significant difference in the univariate analysis, 55.2% of men with OSCC in the present study had advanced clinical staging, while 60.7% of women were diagnosed with early-stage disease. This discrepancy in the clinical stage of the disease between men and women may have influenced the effect of sex on cortisol levels. In a previous study, we found that salivary levels of cortisol but not plasma levels were higher in men than women with oral cancer [22]. Comparing to our previous study, here we used a larger number of OSCC patients which may have contributed to the identification of a significant association between sex and plasma hormone levels in the unadjusted model. There is a variability of results in the literature regarding differences in cortisol secretion between men and women, both under normal [39,40] and stressful situations [41,42]. While some studies show that women [40]; Larsson et al., 2009) or men

[39] exhibit increased systemic levels of cortisol, other studies were unable to demonstrate significant differences between the sexes [41,42]. Kudielka et al. observed increased salivary free cortisol responses to stress in healthy elderly men compared to elderly woman, although there were no differences in plasma cortisol responses to stress between sexes in all age groups [43].

Univariate analysis showed that alcohol consumption was associated with increased systemic cortisol levels in cancer patients. Moreover, in the multiple regression using model 2, abstaining from alcohol was a protect factor for highest cortisol levels in OSCC patients. The relationship between alcohol consumption and HPA axis dysfunction seems to be a two-way street. Although the measurement of cortisol concentrations has been performed in oral cancer patients who were not necessarily under the influence of alcohol at the time of blood collection, evidence suggests that alcohol can directly stimulates HPA axis and glucocorticoid receptors in brain regions (extrahypothalamic, limbic forebrain, and medial prefrontal cortex circuits) contributing to onset and progression of alcohol use disorder [44]. Cortisol in turn may affect the cognitive process and promote habit-based learning, which can contribute to habit formation and relapses [45]. Both HPA axis dysfunction and exposure to stress interact and became a critical component for developing alcohol use disorders [57]. In rodents, heavy alcohol consumption leads to increased levels of cortisol, in addition to changes in HPA axis feedback mechanism [46]. There is still a lack of studies investigating the mechanisms involved in systemic cortisol variation related to alcohol consumption in oncological patients. Our findings also showed that increased cortisol levels were linked with occurrence of regional metastasis in OSCC patients in the univariate analysis. In our previous investigation, although with a smaller sample group, we also observed that advanced-stage OSCC patients displayed increased plasma levels compared to early-stage patients. Pre-clinical investigations suggest that high levels of glucocorticoid both exogenous and that derived from chronic stress could contribute to OSCC progression [47,48]. In addition, *in vitro* results show that glucocorticoid may stimulate the growth of cancer cells [13,49], including OSCC cell lines [14]. On the other hand, in the current study the association between regional metastasis e high cortisol levels has not been maintained in the logistic regression. Indeed, the history of alcohol consumption could be a relevant interfering variable in this relationship and possibly a potential influencer on tumor progression.

Persistent activation of the HPA axis due to prolonged exposure to

stressful events (chronic stress) results in increased cortisol levels [50]. HPA axis activity and abnormal cortisol secretion have been linked to the onset and maintenance of psychological disorders, such as anxiety and depression [50]. Increased cortisol levels are associated with depression and anxiety symptoms in healthy and oncological patients [16–18]. Sharma et al. explored the cortisol levels and psychological symptoms in OSCC patients [51]. The authors observed higher cortisol levels and higher anxiety and depression scores in the oncological patients compared to those with OPMD and health patients [51]. In their study, a small sample of patients were studied, and no association or regression analysis were applied to identify the interaction between hormonal and psychological data. Other studies have evaluated cortisol and anxiety levels in HNC/OSCC patients, separately. Aarstad et al. observed higher anxiety and lower depression levels in HNC patients, when compares to patients with benign HN disease [16]. Previously, we found increased levels of plasmatic and salivary cortisol in OSCC patients compared to healthy volunteers, smokers and drinkers and patients with OPMD [22]. In the current study, global anxiety and depression scores were not predictive for cortisol levels in oral cancer patients. However, we observed that some specific anxiety symptoms were associated with systemic cortisol levels. OSCC patients who reported "fear of losing control" in the BAI had 6.5 times more likely to displaying highest plasma cortisol levels. Cancer diagnosis and fear of treatment are highly stressful and potentially traumatic for the patients [15]. Our results suggest that the feeling of losing control triggered after diagnosis and before cancer treatment could incite diurnal secretion of aberrant cortisol levels. Conversely, BAI symptoms of "hands trembling" and being "nervous" were protector factors for increased cortisol levels in OSCC patients. In the same line, [52] found an inverse correlation between anxiety and salivary cortisol levels in prostate cancer patients. Some anxiety-related symptoms reported in BAI, as hands tremors, are also considered symptoms of alcohol withdrawal syndrome (AWS) [53]. It has been shown that AWS symptoms are directly linked to SNS's hyperactivation [54]. In a previous study, we observed that BAI symptom of hands tremors was associated with higher plasma norepinephrine levels in head and neck squamous cell carcinoma (HNSCC) patients, including patients with oral cancer [23]. These results may suggest that the physical symptoms triggered by anxiety are most likely influenced by catecholamines through SNS activity than by HPA response.

In view of the variability of results inherent to different anxiety symptoms, we hypothesize that there may be a discrepancy between what patients report in BAI and their true mental and emotional state that is really interfering with physiological stress levels such as cortisol secretion. Furthermore, patients may have difficulties to process the psychological changes they are experiencing, affecting the consciousness of their anxiety status. In the logistic regression, depression symptoms measured by the BDI were not predictors for cortisol levels in oral cancer patients. Our results showed that "suicide ideation" was associated with highest levels of cortisol in OSCC patients, however this depression symptom was not an independent predictor for hormone concentrations. A positive correlation between cortisol levels and depression scores has been identified in healthy people [17]. Elevated cortisol concentrations were also linked with depression in patients with malignant ovarian tumors [55] and advanced metastatic cancer [56]. The lack of association between depression and systemic cortisol levels observed in our sample may be associated with the exceptionally low percentage of OSSC patients classified with moderated and severe depression.

This study has some limitations. Cortisol concentrations were analyzed in plasma samples collected once daily (in the morning), so the circadian rhythm of OSCC patients was not analyzed. In addition, plasma cortisol levels were categorized for logistic regression analyses. Hormonal measurement was only performed in the pre-treatment period, making it impossible to know the cortisol secretion profile during and after cancer treatment, or the variables which could influence hormonal levels in these periods. Moreover, we were not able to demonstrate whether systemic cortisol levels have impact on OSCC patient's prognostic. Further studies with oral cancer patients in an appropriate follow-up cut may reveal whether cortisol levels or HPA axis dysregulation affect the global and disease-specific survival. In conclusion, our results reveal that pain, alcoholism, and the feeling of fear of losing control are associated with increased systemic cortisol levels in OSCC patients. Moreover, this is the first evidence that specific anxiety symptoms can act as protective or risk factors to plasma cortisol levels in cancer patients. Psychological intervention, as well as strict pain control and drinking habits management should be considered in the treatment approach of oncological patients. These strategies could lead to greater well-being and prevent negative effects of diurnal cortisol dysregulation on cancer progression.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] P.H. Thaker, S.K. Lutgendorf, A.K. Sood, The neuroendocrine impact of chronic stress on cancer, Cell Cycle 6 (2007) 430–433, https://doi.org/10.4161/cc.6.4.3829.

[2] B. Mravec, M. Tibensky, L. Horvathova, Stress and cancer. Part I: mechanisms mediating the effect of stressors on cancer, J. Neuroimmunol. 346 (2020) 577311, https://doi.org/10.1016/j.jneuroim.2020.577311.

[3] D. Spiegel, J. Giese-Davis, Depression and cancer: mechanisms and disease progression, Biol. Psychiatr. 54 (2003) 269–282, https://doi.org/10.1016/s0006-3223(03)00566-3.

[4] M.H. Antoni, S.K. Lutgendorf, S.W. Cole, F.S. Dhabhar, S.E. Sephton, P. G. McDonald, M. Stefanek, A.K. Sood, The influence of bio-behavioural factors on tumour biology: pathways and mechanisms, Nat. Rev. Cancer 6 (2006) 240–248, https://doi.org/10.1038/nrc1820.

[5] R. Ader, N. Cohen, D. Felten, Psychoneuroimmunology: interactions between the nervous system and the immune system, Lancet 345 (1995) 99–103, https://doi.org/10.1016/s0140-6736(95)90066-7.

[6] M.S. Flint, A. Baum, W.H. Chambers, F.J. Jenkins, Induction of DNA damage, alteration of DNA repair and transcriptional activation by stress hormones, Psychoneuroendocrinology 32 (2007) 470–479, https://doi.org/10.1016/j.psyneuen.2007.02.013.

[7] L. Zhang, J. Pan, W. Chen, J. Jiang, J. Huang, Chronic stress-induced immune dysregulation in cancer: implications for initiation, progression, metastasis, and treatment, Am J Cancer Res. 10 (5) (2020 May 1) 1294–1307.

[8] F.J. Jenkins, B. Van Houten, D.H. Bovbjerg, Effects on DNA damage and/or repair processes as biological mechanisms linking psychological stress to cancer risk, J. Appl. Biobehav. Res. 19 (2014) 3–23, https://doi.org/10.1111/jabr.12019.

[9] V.B. Valente, D. de Melo Cardoso, G.M. Kayahara, G.B. Nunes, K.C. Tjioe, É. R. Biasoli, G.I. Miyahara, S.H.P. Oliveira, G.Z. Mingoti, D.G. Bernabé, Stress hormones promote DNA damage in human oral keratinocytes, Sci. Rep. 11 (1) (2021 Oct 5) 19701, https://doi.org/10.1038/s41598-021-99224-w.

[10] Z. Feng, L. Liu, C. Zhang, T. Zheng, J. Wang, M. Lin, Y. Zhao, X. Wang, A.J. Levine, W. Hu, Chronic restraint stress attenuates p53 function and promotes tumorigenesis, Proc. Natl. Acad. Sci. U.S.A. 109 (2012) 7013–7018, https://doi.org/10.1073/pnas.1203930109.

[11] A. Schrepf, P.H. Thaker, M.J. Goodheart, D. Bender, G.M. Slavich, L. Dahmoush, F. Penedo, K. DeGeest, L. Mendez, D.M. Lubaroff, S.W. Cole, A.K. Sood, S. K. Lutgendorf, Diurnal cortisol and survival in epithelial ovarian cancer, Psychoneuroendocrinology 53 (2015 Mar) 256–267, https://doi.org/10.1016/j.psyneuen.2015.01.010.

[12] J.M. Zeitzer, B. Nouriani, M.B. Rissling, G.W. Sledge, K.A. Kaplan, L. Aasly, O. Palesh, B. Jo, E. Neri, F.S. Dhabhar, D. Spiegel, Aberrant nocturnal cortisol and disease progression in women with breast cancer, Breast Cancer Res. Treat. 158 (2016) 43–50, https://doi.org/10.1007/s10549-016-3864-2.

[13] X.Y. Zhao, P.J. Malloy, A.V. Krishnan, S. Swami, N.M. Navone, D.M. Peehl, D. Feldman, Glucocorticoids can promote androgen-independent growth of prostate cancer cells through a mutated androgen receptor, Nat. Med. 6 (2000) 703–706, https://doi.org/10.1038/76287.

[14] D.G. Bernabé, A.C. Tamae, É.R. Biasoli, S.H. Oliveira, Stress hormones increase cell proliferation and regulates interleukin-6 secretion in human oral squamous cell carcinoma cells, Brain Behav. Immun. 25 (2011) 574–583, https://doi.org/10.1016/j.bbi.2010.12.012.

[15] M.J. Cordova, M.B. Riba, D. Spiegel, Post-traumatic stress disorder and cancer, Lancet Psychiatr. 4 (4) (2017 Apr) 330–338, https://doi.org/10.1016/S2215-0366(17)30014-7.

[16] H.J. Aarstad, A.K. Aarstad, J.H. Heimdal, J. Olofsson, Mood, anxiety and sense of humor in head and neck cancer patients in relation to disease stage, prognosis and quality of life, Acta Otolaryngol. 125 (2005) 557–565, https://doi.org/10.1080/00016480510027547.

[17] Y. Jia, L. Liu, C. Sheng, Z. Cheng, L. Cui, M. Li, Y. Zhao, T. Shi, T.O. Yau, F. Li, L. Chen, Increased serum levels of cortisol and inflammatory cytokines in people with depression, J. Nerv. Ment. Dis. 207 (2019) 271–276, https://doi.org/10.1097/NMD.0000000000000957.

[18] W.P. Chang, C.C. Lin, 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. 29 (2017 Aug) 79–84, https://doi.org/10.1016/j.ejon.2017.05.008.

[19] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA A Cancer J. Clin. 68 (2018) 394–424, https://doi.org/10.3322/caac.21492.

[20] A.C. Chi, T.A. Day, B.W. Neville, Oral cavity and oropharyngeal squamous cell carcinoma–an update, CA A Cancer J. Clin. 65 (2015) 401–421, https://doi.org/10.3322/caac.21293.

[21] M. Kumar, R. Nanavati, T.G. Modi, C. Dobariya, Oral cancer: etiology and risk factors: a review, J. Cancer Res. Therapeut. 12 (2016) 458–463, https://doi.org/10.4103/0973- 1482.186696.

[22] D.G. Bernabé, A.C. Tamae, G.I. Miyahara, M.L. Sundefeld, S.P. Oliveira, É. R. Biasoli, Increased plasma and salivary cortisol levels in patients with oral cancer and their association with clinical stage, J. Clin. Pathol. 65 (2012) 934–939, https://doi.org/10.1136/jclinpath-2012-200695.

[23] D.B. Bastos, B.A.M. Sarafim-Silva, M.L.M.M. Sundefeld, A.A. Ribeiro, J.D. P. Brandão, É.R. Biasoli, G.I. Miyahara, D.E. Casarini, D.G. Bernabé, Circulating catecholamines are associated with biobehavioral factors and anxiety symptoms in head and neck cancer patients, PLoS One 13 (8) (2018 Aug 20), e0202515, https://doi.org/10.1371/journal.pone.0202515.

[24] E.E. Cohen, S.J. LaMonte, N.L. Erb, K.L. Beckman, N. Sadeghi, K.A. Hutcheson, M. D. Stubblefield, D.M. Abbott, P.S. Fisher, K.D. Stein, G.H. Lyman, M.L. Pratt-Chapman, American cancer society head and neck cancer survivorship care guideline, CA A Cancer J. Clin. 66 (3) (2016 May) 203–239, https://doi.org/10.3322/caac.21343.

[25] S. Dunne, O. Mooney, L. Coffey, L. Sharp, D. Desmond, C. Timon, E. O'Sullivan, P. Gallagher, Psychological variables associated with quality of life following primary treatment for head and neck cancer: a systematic review of the literature from 2004 to 2015, Psycho Oncol. 26 (2017) 149–160, https://doi.org/10.1002/pon.4109.

[26] K. Rieke, K.K. Schmid, W. Lydiatt, J. Houfek, E. Boilesen, S. Watanabe-Galloway, Depression and survival in head and neck cancer patients, Oral Oncol. 65 (2017 Feb) 76–82, https://doi.org/10.1016/j.oraloncology.2016.12.014.

[27] M.E. Charlson, P. Pompei, K.L. Ales, C.R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J. Chron. Dis. 40 (1987) 373–383, https://doi.org/10.1016/0021-9681(87)90171-8.

[28] L.H. Sobin, M.K. Gospodarowicz, C.H. Wittekind, International Union against Cancer, TNM Classification of Malignant Tumours, seventh ed., Wiley-Blackwell, Hoboken, 2009.

[29] B.A.M. Sarafim-Silva, G.D. Duarte, M.L.M.M. Sundefeld, É.R. Biasoli, G. I. Miyahara, D.G. Bernabé, Childhood trauma is predictive for clinical staging, alcohol consumption, and emotional symptoms in patients with head and neck cancer, Cancer 124 (2018) 3684–3692, https://doi.org/10.1002/cncr.31597.

[30] A.T. Beck, N. Epstein, G. Brown, R.A. Steer, An inventory for measuring clinical anxiety: psychometric properties, J. Consult. Clin. Psychol. 56 (1988) 893–897, https://doi.org/10.1037//0022-006x.56.6.893.

[31] A.T. Beck, R.A. Steer, Beck Depression Inventory Manual, Psychology Corporation, San Antonio, TX, 1993.

[32] A.W.S. Fung, M.J. Knauer, I.M. Blasutig, D.A. Colantonio, V. Kulasingam, Evaluation of electrochemiluminescence immunoassays for immunosuppressive drugs on the Roche cobas e411 analyzer, F1000Res 13 (2017) 1832, https://doi.org/10.12688/f1000research.12775.2.

[33] R.R. Edwards, T. Kronfli, J.A. Haythornthwaite, M.T. Smith, L. McGuire, G.G. Page, Association of catastrophizing with interleukin-6 responses to acute pain, Pain 140 (2008) 135–144, https://doi.org/10.1016/j.pain.2008.07.024.

[34] P.J. Quartana, L.F. Buenaver, R.R. Edwards, B. Klick, J.A. Haythornthwaite, M. T. Smith, Pain catastrophizing and salivary cortisol responses to laboratory pain testing in temporomandibular disorder and healthy participants, J. Pain 11 (2010) 186–194, https://doi.org/10.1016/j.jpain.2009.07.008.

[35] T. Pincus, A.K. Burton, S. Vogel, A.P. Field, A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain, Spine 27 (2002) E109–E120, https://doi.org/10.1097/00007632-200203010- 00017.

[36] M.J. Bair, E.L. Poleshuck, J. Wu, E.K. Krebs, T.M. Damush, W. Tu, K. Kroenke, Anxiety but not social stressors predict 12-month depression and pain severity, Clin. J. Pain 29 (2013) 95–101, https://doi.org/10.1097/AJP.0b013e3182652ee9.

[37] L.M. Thornton, B.L. Andersen, W.P. Blakely, The pain, depression, and fatigue symptom cluster in advanced breast cancer: covariation with the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, Health Psychol. 29 (2010) 333–337, https://doi.org/10.1037/a0018836.

[38] R. Dev, D. Hui, S. Dalal, Z.I. Nooruddin, S. Yennurajalingam, E. Del Fabbro, E. Bruera, Association between serum cortisol and testosterone levels, opioid therapy, and symptom distress in patients with advanced cancer, J. Pain Symptom Manag. 41 (2011) 788–795, https://doi.org/10.1016/j.jpainsymman.2010.06.021.

[39] T.E. Seeman, B. Singer, C.W. Wilkinson, B. McEwen, Gender differences in age-related changes in HPA axis reactivity, Psychoneuroendocrinology 26 (2001) 225–240, https://doi.org/10.1016/s0306-4530(00)00043-3.

[40] P.J. Gunn, B. Middleton, S.K. Davies, V.L. Revell, D.J. Skene, Sex differences in the circadian profiles of melatonin and cortisol in plasma and urine matrices under constant routine conditions, Chronobiol. Int. 33 (2016) 39–50, https://doi.org/10.3109/07420528.2015.1112396.

[41] M. Kotlyar, P. Thuras, D.K. Hatsukami, M. al'Absi, Sex differences in physiological response to the combination of stress and smoking, Int. J. Psychophysiol. 118 (2017) 27–31, https://doi.org/10.1016/j.ijpsycho.2017.05.008.

[42] S. Helbig, J. Backhaus, Sex differences in a real academic stressor, cognitive appraisal and the cortisol response, Physiol. Behav. 179 (2017) 67–74, https://doi.org/10.1016/j.physbeh.2017.05.027.

[43] B.M. Kudielka, A. Buske-Kirschbaum, D.H. Hellhammer, C. Kirschbaum, HPA axis responses to laboratory psychosocial stress in healthy elderly adults, younger adults, and children: impact of age and gender, Psychoneuroendocrinology 29 (1) (2004 Jan) 83–98, https://doi.org/10.1016/S0306-4530(02)00146-4.

[44] S.K. Blaine, R. Sinha, Alcohol, stress, and glucocorticoids: from risk to dependence and relapse in alcohol use disorders, Neuropharmacology 122 (2017 Aug 1) 136–147, https://doi.org/10.1016/j.neuropharm.2017.01.037.

[45] M.A. Stephens, G. Wand, Stress and the HPA axis: role of glucocorticoids in alcohol dependence, Alcohol Res 34 (2012) 468–483.

[46] K. Ogilvie, S. Lee, B. Weiss, C. Rivier, Mechanisms mediating the influence of alcohol on the hypothalamic-pituitary-adrenal axis responses to immune and nonimmune signals, Alcohol Clin. Exp. Res. 22 (1998) 243S–247S, https://doi.org/10.1097/00000374-199805001-00005.

[47] T. Kage, T. Mogi, Y. Katsumata, T. Yamada, T. Chino, Lung and cervical lymph-nodemetastasis after cortisone enhancement in hamster cheek-pouch carcinogenesis, Arch. Oral Biol. 33 (1988) 459–461, https://doi.org/10.1016/0003- 9969(88)90205-1.

[48] H. Xie, C. Li, Y. He, R. Griffin, Q. Ye, L. Li, Chronic stress promotes oral cancer growth and angiogenesis with increased circulating catecholamine and glucocorticoid levels in a mouse model, Oral Oncol. 51 (11) (2015 Nov) 991–997, https://doi.org/10.1016/j.oraloncology.2015.08.007.

[49] E. Buoso, M. Ronfani, M. Galasso, D. Ventura, E. Corsini, M. Racchi, Cortisol-induced SRSF3 expression promotes GR splicing, RACK1 expression and breast cancer cells migration, Pharmacol. Res. 143 (2019 May) 17–26, https://doi.org/10.1016/j.phrs.2019.03.008.

[50] C. Faravelli, C. Lo Sauro, L. Lelli, F. Pietrini, L. Lazzeretti, L. Godini, L. Benni, G. Fioravanti, G.A. Talamba, G. Castellini, V. Ricca, The role of life events and HPA axis in anxiety disorders: a review, Curr. Pharmaceut. Des. 18 (2012) 5663–5674, https://doi.org/10.2174/138161212803530907.

[51] P. Sharma, S.V. Sandhu, R. Bhandari, I. Verma, R.K. Bhullar, R.K. Khangura, Estimation of cortisol levels in patients with premalignant disorders and oral squamous cell carcinoma, J. Oral Maxillofac. Pathol. 22 (2018) 27–34, https://doi.org/10.4103/jomfp.JOMFP_181_16.

[52] C.F. Sharpley, D.R.H. Christie, V. Bitsika, L.L. Agnew, N.M. Andronicos, M. E. McMillan, T.M. Richards, Neurobiological and psychological evidence of chronic stress in prostate cancer patients, Eur. J. Cancer Care 26 (6) (2017 Nov), https://doi.org/10.1111/ecc.12671.

[53] H.C. Becker, Effects of alcohol dependence and withdrawal on stress responsiveness and alcohol consumption, Alcohol Res 34 (4) (2012) 448–458.

[54] G.L. Kovács, M. Soroncz, I. Tegyei, Plasma catecholamines in ethanol tolerance and withdrawal in mice, Eur. J. Pharmacol. 448 (2–3) (2002) 151–156, https://doi.org/10.1016/s0014-2999(02)01939-8.

[55] S.K. Lutgendorf, A.Z. Weinrib, F. Penedo, D. Russell, K. DeGeest, E.S. Costanzo, P. J. Henderson, S.E. Sephton, N. Rohleder, J.A. Lucci 3rd, S. Cole, A.K. Sood, D. M. Lubaroff, Interleukin-6, cortisol, and depressive symptoms in ovarian cancer patients, J. Clin. Oncol. 26 (29) (2008 Oct 10) 4820–4827, https://doi.org/10.1200/JCO.2007.14.1978.

[56] C.F. Jehn, D. Kuehnhardt, A. Bartholomae, S. Pfeiffer, M. Krebs, A.C. Regierer, P. Schmid, K. Possinger, B.C. Flath, Biomarkers of depression in cancer patients, Cancer 107 (11) (2006 Dec 1) 2723–2729, https://doi.org/10.1002/cncr.2229.

[57] T.S. Schepis, U. Rao, H. Yadav, B. Adinoff, The limbic-hypothalamic-pituitary-adrenal axis and the development of alcohol use disorders in youth, Alcohol Clin. Exp. Res. 35 (2011) 595–605, https://doi.org/10.1111/j.1530-0277.2010.01380.x.