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Eventos traumáticos na infância estão associados com a ocorrência de desordens emocionais e variáveis clinicopatológicas em pacientes com câncer de cabeça e pescoço

Araçatuba – São Paulo

2017

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Orientador: Prof. Ass. Dr. Daniel Galera Bernabé

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Epígrafe

"O sucesso nasce do querer, da determinação e persistência em se chegar a um objetivo. Mesmo não atingindo o alvo, quem busca e vence obstáculos, no mínimo fará coisas admiráveis".

José de Alencar

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RESUMO

Introdução: Eventos traumáticos na infância têm sido associados à ocorrência de ansiedade e depressão na fase adulta. Esta relação tem sido investigada em pacientes com câncer de mama, mas pouco explorada em pacientes com outros tipos de câncer. **Objetivo:** Avaliar a ocorrência de eventos traumáticos na infância e sua associação com as características clinicopatológicas e desordens emocionais em pacientes com câncer de cabeça e pescoço (CCP). **Método:** Foram incluídos no estudo 110 pacientes com diagnóstico de carcinoma espinocelular (CEC) de cabeça e pescoço antes de iniciar o tratamento oncológico. Dados clinicopatológicos e biocomportamentais foram coletados dos prontuários clínicos dos pacientes. Os níveis de ansiedade e depressão foram avaliados por meio do Inventário de Ansiedade de Beck (IAB) e o Inventário de Depressão de Beck (IDB), respectivamente. Questionário sobre Trauma na Infância (CTQ) foi utilizado para avaliar a ocorrência de eventos traumáticos na infância. **Resultados:** A maioria dos pacientes eram homens (88,2%) com tumores localizados na boca (65.6%), laringe (19%) e orofaringe (15.4%). Cento e cinco pacientes (95.5%) relataram pelo menos um tipo de experiência traumática na infância. A negligência emocional foi o subtipo de trauma mais reportado (43.8%) e análise multivariada revelou que ela foi uma variável independente para estadiamento clínico avançado (β=2.15, p=0.048) e maior consumo de álcool (β=2.32, p=0.031). Pacientes com CCP que tiveram maior ocorrência de trauma na infância apresentaram quase 12 vezes mais chance de

apresentar níveis elevados de depressão durante o período pré-tratamento (β=11.89; p=0.0002). A ocorrência de negligência física na infância foi preditiva para aumento dos níveis de ansiedade (β=4.17; p=0.029). **Conclusão:** Eventos traumáticos na infância são preditivos para o estadiamento clínico avançado, consumo de álcool e sintomas psicológicos em pacientes com câncer de cabeça e pescoço e devem ser consideradas nas estratégias de intervenção clínica e psicológica durante o tratamento oncológico.

Palavras-chave: Câncer, Trauma Psicológico; Adultos Sobreviventes de Eventos Adversos na Infância; Neoplasias de Cabeça e Pescoço; Depressão, Ansiedade.

Sarafim-Silva BAM. Childhood traumatic events are associated with occurrence of emotional disorders and clinicopathological variables in head and neck cancer patients.[dissertation]. Araçatuba: UNESP - São Paulo State University; 2017.

ABSTRACT

Introduction: Childhood Traumatic events have been associated with anxiety and depression occurrence in adulthood. This relationship has been investigated in breast cancer patients, however it is little explored in patients with other types of cancer. **Objective:** To evaluate the childhood trauma occurrence in head and neck cancer (HNC) patients, as well as its association with clinicopathological variables, and anxiety and depression levels. **Method:** The study included 110 head and neck squamous cell carcinoma (HNSCC) patients before starting cancer treatment. Clinicopathological and biobehavioral data were collected from patient's medical records. Anxiety and depression levels were assessed by Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI), respectively. Childhood Trauma Questionnaire (CTQ) was used to evaluate the childhood traumatic events occurrence. **Results:** The most of the HNSCC patients was men (88.2%), with tumors located in oral cavity (65.6%), larynx (19%) and oropharynx (15.4%). One hundred and five patients (95.5%) had experienced at least one type of childhood trauma. Emotional neglect was the most reported childhood trauma (43.8%) and multiple regression revealed that it was an independent variable for advanced clinical staging (β=2.15, p=0.048), and higher alcohol consumption (β=2.32, p=0.031). HNSCC patients who had a higher occurrence of traumatic events in childhood had almost 12 times more chances of having increased depression levels during the pre-treatment period (β=11.89; p=0.0002). Childhood physical neglect occurrence was a predictive factor for

increased anxiety levels (β = 4.17, p = 0.029). **Conclusion:** Childhood traumatic events are predictive for advanced clinical staging, alcohol consumption, and emotional disorders in HNSCC patients, and should be considered in clinical and psychological intervention strategies during cancer treatment.

KEYWORDS: Psychological Trauma; Adult Survivors of Child Adverse Events; Head and Neck Neoplasms

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Lista de Abreviaturas

HNC – Head and Neck Cancer

HNSCC – Head and Neck Squamous Cell Carcinoma

SCC – Scamous Cell Carcinoma

CCI – Charlson Comorbidity Index

AVS – Visual Analog Scale

UICC – International Union for Cancer Control

CTQ – Childhood Trauma Questionnaire

BAI – Beck Anxiety Inventory

BDI – Beck Depression Inventory

CTS – Childhood Trauma Subtypes

Sumário

Childhood traumatic events are associated with occurrence of emotional disorders and clinicopathological variables in head and neck cancer patients.

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Normalization according to the periodic Head & Neck (Anexo B)

1. Introduction*

Cancer patients may experience high levels of stress, anxiety and depression during and after disease diagnosis and treatment.[1-3] Emotional disorders have particular relevance in head and neck cancer (HNC) patients.[4-8] Ocurrence and treatment of HNC such as malignant tumors located in the oral cavity, oropharynx and larynx, may induce facial disfigurement, chewing and swallowing dysfunctions, phonation deficit, pain (more intense than other types of cancer) and fear of death.[8-11] As human social interaction and emotional expression depend largely of structural and functional integrity of thead and neck region, the HNC diagnosis and treatment have a significant psychological impact.[7-13]

Studies have shown that emotional disorders affect the quality of life, the immunological function and the survival time of cancer patients.[11,13,14] HNC patients display high levels of anxiety, depression and mood swings.[8,15-17] Aarstad et al.[18] observed that head and neck squamous cell carcinoma (HNSCC) patients with regional lymph node metastasis had higher anxiety levels than patients who had the disease at an initial stage.[18] Another study, carried out with oral cancer patients, showed that increased anxiety levels was associated with difficulty in deal with the disease diagnosis and higher prevalence of distress.[19] Other investigations have also revealed that HNSCC patients with higher levels of anxiety and depression exbihit worse quality of life,[20,21] lower adherence to treatment and worse prognosis.[22] These findings indicate the need for diagnosis and management of emotional disorders in HNC patients, as well as the identification of their risk factors.

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*Normas da revista Head & Neck

Stressor events experienced in childhood, mainly emotional neglect, are risk factors for development of emotional disorders in adulthood.[23-25] Childhood trauma not only increases the vulnerability for anxiety and depression occurrence, it is also associated with a more chronic levels of these disorders.[23] Psychological trauma is an event experienced or witnessed by the individual, in which there was a threat to life or physical integrity of himself or of persons affectively linked to him.[26-28] Traumatic events may produce irreparable emotional damage and prolonged suffering.[27-30] Few investigations have explored the occurrence of childhood trauma events in cancer patients.[31-39] Almost all of them were conducted in breast cancer patients.[31-39] The first study exploring childhood trauma ocurrence in cancer patients was carried out in 2006 by Salmon et al.[31] The authors observed a significant association between childhood trauma with cancer-related psychological sympthoms, such as self-blame, bodily shame and stress in women diagnosed with breast cancer.[31] Goldsmith et al.[32] analyzed the association between stress symptoms and adverse experiences during childhood in breast cancer patients.[32] The women who reported suffering emotional and sexual abuse during childhood displayed higher symptoms of negative thoughts related to cancer and difficulties in deal with stressors events, such as cancer diagnosis.[32] In other studies, history of child abuse and neglect in the childhood were correlated with worse quality of life and higher intensity of cancer-related fatigue in breast cancer survivors.[33-35] In turn, Crosswell et al.[36], showed that psychological trauma in childhood can be associated with a deregulated systemic levels of cancer progression-related cytokines.[36] In more recent studies, childhood trauma was associated with increased symptoms of fatigue, depression, and stress during the breast cancer treatment[37] and worse emotional

response to cancer.[38] So far, only one study has investigated the occurrence of childhood trauma in HNC patients.[39] Archer et al.[39] found that HNSCC patients reported higher adversity in childhood and higher levels of depression than colorectal cancer patients. However, authors were cautious about these results, to being a preliminary study, and with low casuistry.[39]

Emotional responses in cancer patients may also affect the adherence to treatment, immunological response to primary tumor and metastasis, as well as the maintenance of biobehavioral risk factors, such as smoking and alcoholism.[19,20,40,41] However, little is known about the factors which could influence psychological and biobehavioral variables in cancer patients, especially in HNC. In this context, there are increasing evidences showing that psychological characteristics of individuals with or without cancer are influenced by traumatic events experienced during childhood.[31-39] However, there are no evidences of association between childhood trauma ocurrence and clinicopathological profile in HNSCC patients. In the present study, we have analyzed the occurrence of childhood trauma in HNSCC patients, as well as its association with emotional disorders and clinicopathological variables.

2. Patients and Methods

2.1 Ethics statements

This study was approved by the human studies committee of the Araçatuba Dental School, São Paulo State University (UNESP). Informed consent was obtained from all participants. Participants were not paid for their participation in the study. Review board requirements for written informed consent were waived because all personal identifying information was removed from the dataset prior to analysis.

2.2 Patients

The study included patients with definitive diagnosis of HNSCC registered in the Oral Oncology Center, Araçatuba Dental School, São Paulo State University (UNESP), without distinction of ethnic origin, religious, professional and marital status. Patients who completed the following criteria were included: histopathological diagnosis of squamous cell carcinoma (SCC) without any previous treatment; tumors located in the oral cavity, oropharynx or larynx; and never have been treated for cancer. There were excluded patients with previous diagnosis of cancer. A total of 110 patients (72 oral SCC, 21 larynx SCC, and 17 oropharyngeal SCC) were included. Sociodemographic and clinical variables such as age, gender, marital status, family income, education, lives with someone, number of children, dental condition, comorbidity, intensity of pain related to primary tumor, sleep quality, tumor location, clinical staging and history of cigarette and alcohol consumption were collected from the patient's medical records. Comorbidity ocurrence and serverity was assessed according to the Charlson Comorbidity Index (CCI). This method classifies the severity of some

clinical conditions generating a final score that evaluates the weight of the patient's morbidity. The presence and intensity of pain at the tumor site was estimated by the visual analog scale (AVS) which classifies pain intensity from zero (absence of pain) to 10 (maximum intensity of pain). Sleep self-report were obtained at the same day of interview and information such as quality of sleep experience over the last night and last week were reported. The sleep quality was graded according to five subscales: very good, good, regular, bad and terrible. The tobacco and alcohol consumptions were graded in abstainers, light (until 10 cigarettes and 1-2 doses, per day), moderate (11 to 20 cigarettes and 3-4 doses, per day), and heavy (more of 20 cigarettes and more of 4 doses, per day). The clinical staging followed the criteria of the UICC.[42] The patients were submitted to specific psychological tests to evaluate the occurrence of childhood traumatic events, as well as the anxiety and depression levels.

2.3 Childhood Trauma Questionnaire (CTQ)

The CTQ was used to investigate the occurrence and frequency of traumatic events in childhood period. CTQ evaluates the occurrence of abuse and neglect in childhood.[43] Initially the CTQ contained 70 items which assessed physical, sexual and emotional abuse and neglect in childhood.[43] Subsequently, it was reviewed and a reduced version containing 28 questions (CTQ-28) was made.[43,44] For the present study we have used a version translated and validated to portuguese in 2006.[44] The instrument has a rating ranging from 1 to 5 scores: 1 (never), 2 (few times), 3 (sometimes), 4 (oftentimes) and 5 (always). The evaluation was made according to five subscales of traumatic events: physical abuse, emotional abuse, sexual abuse, physical neglect and emotional neglect

and a scale of minimization/negation of responses.[44] Patients were encouraged to be true in answers.

2.4 Beck Anxiety Inventory (BAI)

The anxiety levels of HNSCC patients were assessed by Beck Anxiety Inventory (BAI). BAI is an inventory with 21 items which evaluate the occurrence of anxiety symptoms.[45] If someone symptoms have occurred, the patient should evaluate the its intensity. The severity levels of symptom are graded in 4 scores: 1 (absolutely not), 2 (a little), 3 (moderately) and 4 (severely). The possible range of total score goes from 0 to 63. The instrument makes it possible to identify the intensity of anxiety symptom which range from minimal to severe.[45]

2.5 Beck Depression Inventory (BDI)

Beck Depression Inventory (BDI) was used to investigate the depression levels. BDI measures the intensity of depressive episodes.[46] The instrument contains 21 questions regarding how the individual felt in the last week. The scale contains four possible responses according to intensity of depressive symptoms.[46] The intensity of depression symptoms was graded in 4 levels: minimum, light, moderate and severe.[46]

2.6 Statistical analysis

The program Epi Info™ version 7 was used to perform univariate analyses. The data were checked for normality, and Chi-Square Test and Fisher's Exact Test were used to evaluate the association between the overall CTQ score and the five childhood trauma subtypes with clinicopathological variables, as well as the anxiety and depression levels of HNSCC patients. The median of overall CTQ score was also used to grade the childhood occurrence in higher occurrence and lower occurrence. To analyze the correlation between childhood trauma subtypes (CTS) and psychological and clinicopathological variables, two different measures were used: the first measure consisted in presence or absence of each CTS; and the second measure was defined according to trauma subtype intensity of occurrence: no (score 5), mild (6-10), moderate (11-15) and intense (16-25). Anxiety and depression levels were analyzed following two classifications. First, the four intensity levels were used (minimum, mild, moderate and severe). After, the HNSCC patients were classified in less anxious/depressive (those who had minimum and mild levels scores) or more anxious/depressive (moderate and severe levels). Multivariate regression analysis was performed via stepwise method of elimination considering the psychological and clinicopathological data as a dependent variables and childhood trauma as explanatory. The values of $p<0.05$ were considered significant for all analyses.

3. Results

3.1 Epidemiological and clinicopathological characteristics

One hundred and ten HNSCC patients met inclusion criteria, of whom 72 (65.6%) had tumors located in oral cavity, 21 (19%) in larynx and 17 (15.4%) in oropharynx. HNSCC patient's clinicopathological characteristics are showed in Table 1. The majority of the patients was men (88.2%), of middle age (65.5%), married (66.4%) and 90% had at least 2 children. Only 13.6% lived alone, while 86.4% were residing with their partner and children. The most reported educational level was elementary school (59.1%) and only 5.5% had university. 31.8% of the patients were total edentulous. Most of the patients (57.3%) had family income of 2 to 5 monthly salaries and 60.9% had at least one type of comorbidity. The most common comorbities were hypertension (36.4%), gastritis (13.6%) and diabetes (9.1%). When the Charlson Comorbidity Index (CCI) was evaluated, 40% of patients were graded with score 1, 11.8% with score 2, 5.5% with score 3 and 3.6% had severe comorbidities (score 4). Regarding disease's clinical staging, 60.9% had early stage and 39.1% advanced stage. When primary tumor size was classified, 67.3% of patients displayed T1 and T2 tumors, while 32.7% had larger tumors (T3 and T4). Regional lymph node metastasis was found in 27.3% of patients. Thirty-four patients (30.9%) reported pain related to primary tumor, which were classified in minimum (3.6%), moderate (10.9%), and intense (16.4%). Most of HNSCC patients reported a good sleep quality during the night before interview (46.4%), 19.1% considered sleep as regular, while 14.5% of patients reported a bad or terrible sleep quality (Table 1).

Table 1. HNSCC patients' clinicopathological characteristics.

Variables	*n (%)*
Gender	
Male	97 (88.2)
Female	13 (11.8)
Age range (years)	
0-45	9 (8.1)
46-65	72 (65.5)
> 65	29 (26.4)
Marital status	
Single	18 (16.4)
Married	73 (66.4)
Divorced	13 (11.8)
Widowed	6 (5.4)
Live alone	
No	95 (86.4)
Yes	15 (13.6)
Education	
Illiterate	2 (1.8)
Incomplete primary	16 (14.5)
Elementary school	65 (59.1)
High school	21 (19.1)
University	6 (5.5)
Income (R$/month)	
0,00	10 (9.1)
< 1,000	29 (26.4)
1,100 – 5,000	63 (57.3)
> 5,000	8 (7.2)
Tumor location	
Oral Cavity	72 (65.6)
Larynx	21 (19)
Oropharynx	17 (15.4)
T – classification	
T1	25 (22.7)
T2	49 (44.5)
T3	17 (15.5)
T4	19 (17.3)
Regional metastasis	
N0	80 (72.7)
N+	30 (27.3)
Clinical stage	
I	23 (20.9)
II	44 (40)
III	7 (6.4)
IV	36 (32.7)

CCI score*	
0	43 (39.1)
1	44 (40)
2	13 (11.8)
3	6 (5.5)
4	4 (3.6)
Comorbidity type	
Hypertension	40 (36.4)
Gastritis	15 (13.6)
Diabetes	10 (9.1)
Others	45 (40.9)
Pain intensity	
No	76 (69.1)
Minimum	4 (3.6)
Moderate	12 (10.9)
Intense	18 (16.4)
Sleep quality	
Very good	22 (20)
Good	51 (46.4)
Regular	21 (19.1)
Bad	13 (11.8)
Terrible	3 (2.7)

*CCI: Charlson Comorbidity Index;

2. Tobacco and alcohol use profile

The majority of HNSCC patients (58.2%) was current smokers (table 2). Of these patients, 34.5% were light smokers, 35.5% moderate smokers, and 14.5% were heavy smokers (more than 20 cigarettes per day). Regarding alcohol consumption, 60% were current drinkers. Forty-five patients (40.9%) were light drinkers, 20.9% moderate drinkers and 23.6% heavy drinkers (Table 2).

Table 2. Tobacco and alcohol use profile

Variables	***n (%)***
Smoking	
No	17 (15.4)
Current smoker	64 (58.2)
Ex-smoker	29 (26.4)
Tobacco intensity	
Light	38 (34.5)
Moderate	39 (35.5)
Heavy	16 (14.5)
Alcoholism	
No	15 (13.6)
Current drinker	66 (60)
Ex-drinker	29 (26.4)
Alcohol intensity	
Light	45 (40.9)
Moderate	23 (20.9)
Heavy	27 (23.6)

3. Anxiety, depression and childhood trauma ocurrences in HNSCC patients.

Most of the HNSCC patients (70.9%) displayed minimum level of anxiety, 18.2% mild level, 10% moderate, and only 0.9% showed severe level measured by BAI (table 3). When the patients were assessed by BDI, 67.3% reported a minimum level of depressive sympthoms, followed by 16.4% with mild level, 13.6% with moderate level and the minority (2.7%) displayed severe depression (table 3). The vast majority of the HNSCC patients (95.5%) had experienced at least one type of childhood trauma. The most commonly childhood trauma reported in CTQ was emotional neglect (43.8%), followed by the childhood physical abuse (30.5%), childhood emotional abuse (15.2%) and childhood physical neglect (8.6%). Only two patients (1.9%) reported sexual abuse (Table 3).

Table 3. Anxiety, depression and childhood trauma in HNSCC patients

Variables	*N (%)*
BAI*	
Minimum	78 (70.9)
Mild	20 (18.2)
Moderate	11 (10)
Severe	1 (0.9)
BDI*	
Minimum	74 (67.3)
Mild	18 (16.4)
Moderate	15 (13.6)
Severe	3 (2.7)
Childhood Trauma	
No	5 (4.5)
Yes	105 (95.5)
Types of Childhood Trauma	
Emotional neglect	46 (43.8)
Physical abuse	32 (30.5)
Emotional abuse	16 (15.2)
Physical neglect	9 (8.6)
Sexual abuse	2 (1.9)

**BAI beck anxiety inventory, BDI beck depression inventory*

4. Associations between childhood trauma and clinicopathological variables in HNSCC patients.

Univariate analyses showed that HNSCC divorced patients and patients living alone reported a higher childhood trauma occurrence compared to single and married patients (p=0.044) and those who lived with some member of family (p=0.033), respectively (Table 4). There were not found significant associations between overall CTQ score and age, gender, family income, education, number of children, dental condition, CCI score, intensity of pain, sleep quality, tumor location, clinical staging and intensity of cigarette and alcohol consumption (p>0.05) (Table 4). When the associations between clinicopathological variables and childhood trauma subtypes were analyzed, HNSCC patients who had medical history of gastritis (p=0.033) and diabetes (p=0.035) had higher childhood emotional abuse occurrence compared to patients with negative history for these diseases. The edentulous HNSCC patients also displayed higher exposure to emotional abuse compared to dentate patients (p=0.013). Association between the occurrence of this childhood trauma subtype and clinicopathological variables was also evaluated by univariate analysis. The results showed that HNSCC patients who had lower educational level (p=0.039) and worse sleep quality (p=0.003) reported higher occurrence of childhood emotional abuse. HNSCC patients with smaller tumors in T classification reported higher childhood emotional abuse level compared to larger tumors patients (p=0.043).

The occurrence of childhood emotional neglect was correlated with higher alcohol consumption (p=0.038). Occurrence of childhood emotional neglect was associated with low income (p=0.037) and worse sleep quality (p=0.006).

HNSCC patients who had larger tumor size and regional lymph node metastasis reported increased occurrence of childhood emotional neglect compared to patients with initial tumor (p=0.007) and without metastases (p=0.047), respectively. HNSCC drinkers had higher occurrence of childhood emotional neglect than non-drinkers patients (p=0.025). Patients with larger tumors and higher pain levels reported higher occurrence of childhood emotional neglect compared to patients with smaller tumors (p=0.020) and lower pain levels (p=0.019), respectively.

HNSCC patients who experienced childhood sexual abuse reported worse sleep quality than patients who did not report childhood sexual abuse ocurrence (p=0.033). Childhood physical abuse history was associated with advanced tumor (p=0.007) and advanced clinical staging (p=0.004). Higher occurrence of childhood physical abuse were also correlated with higher alcohol consumption (p=0.009) and advanced clinical staging (p=0.037). Lastly, low-income was correlated with occurrence of childhood physical neglect (p=0.034). HNSCC patients who reported higher intensity of occurrence of this trauma type had lower cancer pain levels (p<0.0001) (table 4).

Table 4. Associations between clinicopathological variables and childhood trauma in HNSCC patients from univariate analysis.

	Overall CTQ Score	Emotional Neglect	Emotional Abuse	Physical Abuse	Physical Neglect	Sexual Abuse
Marital status	0.044*	0.475	0.748	0.643	0.865	0.848
Live alone	0.033*	0.279	0.439	0.219	0.567	0.249
Gastritis	0.102	0.266	0.033*	0.501	0.567	0.076
Diabetes	0.132	0.136	0.035*	0.545	0.508	0.169
Dentition	0.212	0.797	0.013*	0.903	0.299	0.819
Education	0.081	0.424	0.039*	0.561	0.072	0.279
Income	0.208	0.037*	0.786	0.864	0.034*	0.616
T-classification	0.816	0.007*	0.043*	0.007*	0.112	0.572
Reg. Meta.$^{\pi}$	0.326	0.047*	0.491	0.077	0.211	0.256
Clinical stage	0.484	0.264	0.271	0.004*	0.462	0.770
Pain	0.740	0.019*	0.565	0.623	<0.0001*	0.721
Sleep quality	0.146	0.006*	0.003*	0.668	0.396	0.033*
Alcoholism	0.354	0.025*	0.458	0.411	0.115	0.242
Alcohol cons.$^{\mu}$	0.160	0.038*	0.633	0.009*	0.164	0.350

**Values are considered statistically significant at p<0.05 (Chi Square Test or Fisher's exact tests)*
$^{\pi}$*Regional metastasis*
$^{\mu}$*Alcohol consumption*

Multivariate analysis was performed to investigate whether CTQ scores were predictives for clinicopathological variables in HNSCC patients (Table 5). The results showed that childhood emotional neglect was an independent variable for advanced clinical staging at the moment of disease diagnosis (β=2.15, p=0.048) (table 5). The childhood emotional neglect was also predictive for higher alcohol consumption (β=2.32, p=0.031). Patients with occurrence of childhood sexual abuse presented worse sleep quality the night before the interview than patients without a history of this trauma (β=3.37, p=0.017). Multivariate analysis did not evidence significant associations between overall CTQ scores and clinicopathological variables.

Table 5. Childhood trauma subtypes as independent variables for clinicopathological features in HNSCC patients.

	Independent Variables					
	Emotional Neglect			Sexual Abuse		
Dependent Variables	***β***	***95% CI***	***P value****	***β***	***95% CI***	***P value****
Clinical staging	2.15	1.003–4.605	0.048	-	-	-
Alcohol cons.[μ]	2.32	1.083–4.999	0.031	-	-	-
Sleep quality	-	-	-	3.37	1.160–9.825	0.017

[μ] *Alcohol consumption*

6. Associations between childhood trauma and anxiety and depression levels in HNSCC patients.

HNSCC patients experiencing more intense depressive symptoms displayed higher occurrence of childhood trauma measured by CTQ (p=0.001) (table 6). No association was found between overall CTQ score and anxiety levels in the univariate analysis. Anxiety and depression levels in HNSCC patients were correlated to CTQ trauma subtypes. Higher anxiety levels rwere associated with occurrence of sexual abuse (p=0.043) and physical neglect (p=0.002) in childhood. Emotional and physical abuse and emotional neglect in childhood were not correlated with anxiety levels (p>0.05). Univariate analyses showed a significant association between depressive symptoms and all CTQ trauma subtypes, except sexual abuse. More depressive HNSCC patients had a higher occurrence (p=0.041) and intensity (p=0.013) of emotional abuse in childhood compared to less depressive HNSCC patients. However, for childhood emotional neglect, this relationship was inverse with the less depressive patients reporting a higher intensity of occurrence of childhood emotional neglect (p=0.020). Higher occurrence of childhood physical abuse was associated with increased depressive levels (p=0.016). Ocurrence and frequency of childhood physical neglect were also positively correlated to depressive symptoms in HNSCC patients (p<0.05) (table 6).

Table 6. Associations between psychological variables and childhood trauma in HNSCC patients from univariate analysis.

	BAI	BDI
Overall CTQ score	0.175	0.001*
Emotional Neglect	0.353	0.020*
Emotional Abuse	0.093	0.013*
Physical Abuse	0.799	0.016*
Physical Neglect	0.002*	0.026*
Sexual Abuse	0.043*	0.232

**Values are considered statistically significant at p<0.05 (Chi Square Test or Fisher's exact tests)*

Multivariate analysis showed that childhood physical neglect was an independent psychological variable for higher intensity of anxiety symptoms. HNSCC patients who had experienced childhood physical neglect had 4.170 times more likely to display high anxiety levels during the pre-treatment period (β=4.17; p=0.029) (table 7). Multiple regression also showed that higher childhood trauma occurrence was predictive for depressive symptoms in HNSCC patients (β=2.59; p=0.021). When the depression level was defined as response variable , HNSCC patients who had a higher occurrence of traumatic events in childhood displayed almost 12 times more chance of having increased depression levels (β=11.89; p=0.0002) (table 7).

Table 7. Childhood trauma as predictive factor for anxiety and depression levels in HNSCC patients

	Independent Variables					
	Overall CTQ score			Physical Neglect		
Dependent Variables	***β***	***95% CI***	***P value***	***β***	***95% CI***	***P value***
BAI	-	-	-	4.17	1.063-16.357	0.029
BDI	11.89	2.580-54.792	0.0002	-	-	-

Discussion

Clinical studies in the last decade have supported a strong correlation between childhood trauma occurrence and emotional disorders, such as stress, anxiety and depression.[23,24,47-50] The results of the present study revealed that the vast majority of HNSCC patients (95%) experienced at least one type of childhood traumatic event. According to our knowledge, this is the first study which have demonstrated childhood trauma occurrence in almost all individuals of a cancer patients' sample. Crosswell et al.,[36] for example, found an occurrencce of 61% of childhood trauma in breast cancer patients using CTQ. Other studies with breast cancer stimated that less than 60% of the patients' sample reported some type of childhood trauma.[31-35,37,38] Archer et al.[39] investigated the ocurrence of childhood trauma in a sample composed by head neck and colorectal patients. Although the childhood trauma occurrence had been associated with depression levels in HNC patients, the study did not report the global rate of trauma occurrence, and also there were no information regarding the primary site location and histologycal type of the head and neck tumors.[39] In addition, the CTQ trauma subtypes occurrence were not reported in this stydy. Like our study, almost all studies which have evaluated childhood trauma history in cancer patients used the CTQ instrument.[31-35,37-39] The differences of rate of childhood trauma occurrence reported in our study and others with cancer patients may be related to the ethnic and cultural differences between the populations assessed and the phase of oncological follow-up at which the interview is performed. The sample's profile (eg. gender differences) could also be an influencing factor, both to the childhood trauma incidence as to the answers from the psychological interview. Our results also showed that emotional neglect was the most common

childhood trauma subtype in HNSCC patients, while sexual abuse was the least recurrent. These results are in agreement with other investigations.[31-39] These findings may be correlated with the stigma which is still common in society on addressing sexuality. Traumatic events associated to emotional neglect or abuse, such as physical abuse, verbal aggression, or affection lack, are more accepted and make it easier to be exposed during psychological investigation.

Cancer patients may display high anxiety and depression levels at the moment of diagnosis and during disease treatment.[15,18,19,21] Our results showed that patients who reported a higher childhood trauma occurrence had almost 12 times more chance of developing higher depression levels at the moment of tumor diagnosis. This result is in line with finding found by Archer et al.[39] who showed that higher childhood adversity influenced the depression levels of head neck cancer patients before and after treatment.[39] Breast cancer women reporting increased childhood traumatic events exposure also display high depression levels.[33-38] Investigations have also revealed that breast cancer patients with history of childhood trauma exhibit higher cancer-related fatigue levels and worse quality of life after the start of cancer treatment than women without childhood trauma exposure.[35-37] Fagundes et al.[33] observed that childhood trauma not only induces emotional distress, but may also affect the response to breast cancer treatment.[33] In a recent study, the authors noted that anxiety, depression, and childhood emotional neglect were independent variables for worse adjustment to cancer in breast cancer patients.[38] Whereas increased depression symptoms have been observed in HNSCC patients and associated with poor quality of life and worse disease prognosis, [51,52] our results evidencing childhood trauma as a risk factor for depression bring relevant

understanding to be considered in patient psychological support during cancer treatment.

Our results also showed an association between physical negligence and high anxiety levels in HNSCC patients. Emotional neglect has been pointed out as a predictive psychological event of anxiety and worse quality of life during cancer treatment.[33,34] A recent study with breast cancer patients showed that emotional abuse was an independent variable for the occurrence of mild and moderate levels of anxiety.[38] Our study was the first to find association between childhood trauma and increased levels of anxiety in HNSCC patients. This association also has been observed in non-cancer populations.[53-55] In one large study, the researchers investigated the childhood trauma effects on physical and emotional health.[54] The results revealed that childhood trauma experiences predispose humans to a worse quality of life, making them more vulnerable to physical and emotional disorders.[54] Jonker et al.[56] also evaluated the association between childhood traumatic events and anxiety disorder in a large sample. The results showed that childhood traumatic events were a risk factor for anxiety disorders in young adults.[56] In turn, Belli et al.[57] showed that emotional neglect, physical abuse and childhood sexual abuse history were predictive of high anxiety levels in drug users.[57]

When the clinicopathological data from HNSCC patients were correlated with childhood trauma, multiple regression results showed that emotional neglect was predictive of advanced clinical staging. To our knowledge, the present study is the first to explore the association between childhood trauma occurrence and clinical staging at the moment of disease's diagnosis in cancer patients. A possible explanation for the association found between childhood emotional

neglect and advanced clinical staging, is that the patients with childhood emotional neglect history could delay more time to seek treatment after noting the first signal or symptom of primary tumor.. Studies have pointed out the feeling of fear as one of the main factors which led to the cancer diagnosis delay.[58-64] In our hypothesis, childhood trauma occurrence, mainly emotional neglect could intensify the feeling of fear in adulthood, corroborating so that the patient to seek medical care late, and have more advanced disease at diagnosis. Other factors such as low income,[58,61,65] low level of education[61,63], and not be in a relationship[63] and low social support[62,65] have been associated with delay in seeking health care.[61-65] In our study, there was a significant positive association between higher occurrence of childhood trauma and low income, low education, and be divorced or widowed. Although these variables may also be indirectly influencing the effects of childhood trauma on the delay of our patients in seeking health care after they note the tumor, further studies are needed to explore directly the association between childhood trauma experiences and delay in cancer diagnosis.

Our results also demonstrated that childhood emotional neglect was predictive of excessive alcohol consumption in HNSCC. There are strong evidences showing that childhood trauma history predisposes the individual to alcoholism.[66-70] An interesting study revealed that childhood trauma patients started the alcohol addiction earlier than patients without trauma.[67] The study also showed that patients who had experienced childhood trauma had less time for dependence (time between starting alcohol consumption and dependence).[67] Studies in cancer patients demonstrate significant correlation between emotional disorders and alcohol consumption.[71,72] HNSCC patients with high anxiety and

depression levels are heavier drinkers than patients without these emotional disorders.[71,72] Our study was the first to find a direct correlation between childhood trauma and heavy alcohol consumption in HNSCC patients. The negative consequences of high alcohol consumption after diagnosis and during cancer treatment on the patient's prognosis are well known.[71,72] When alcohol consumption is associated with tobacco use in HNSCC patients, the chances of relapse or occurrence of second primary tumors are potentialized.[71,72] Deleviannis et al.[71] showed that HNSCC patients who continue to drink after disease diagnosis had a two times more chance to die of cancer. Another study showed that risk of HNSCC recurrence was associated with alcohol consumption.[72] In view of our results, childhood trauma should be included as a potential risk factor for high alcohol consumption in HNSCC patients, which may have a relevant impact on disease progression.

The present study has some limitations. First, the study had no a healthy control group, which makes it difficult to know if the occurrence of childhood trauma events is more frequent or not in HNSCC patients. The second limitation is related to method used to investigate childhood trauma. The traumatic memory of is not always conscious for the patient compromising the diagnosis of adverse events occurred during childhood. Moreover, patients may not feel comfortable for reporting the traumatic event. Although CTQ is the most used questionnaire worldwide to evaluate childhood trauma, other aspects of the child's environment, such as residential changes, be presence in discussions between parents or family members, changes of school or teachers, and lack of routines or other less intense events[36] were not analyzed. These events may be associated with

psychological well-being and with the commitment of the patient's emotional factors in adulthood.[36]

Overall, our results show that childhood trauma, emotional neglect especially, is a risk factor for the emotional disorders occurrence, such as anxiety and depression in HNSCC patients. Moreover, for the first time it was evidenced that childhood trauma is predictive for advanced clinical staging, and high levels of alcohol consumption in in this population. Our study represents an important step to understand the effects of childhood trauma in cancer patients. In view of our results, childhood trauma history should be considered in clinical and psychological intervention strategies during cancer treatment.

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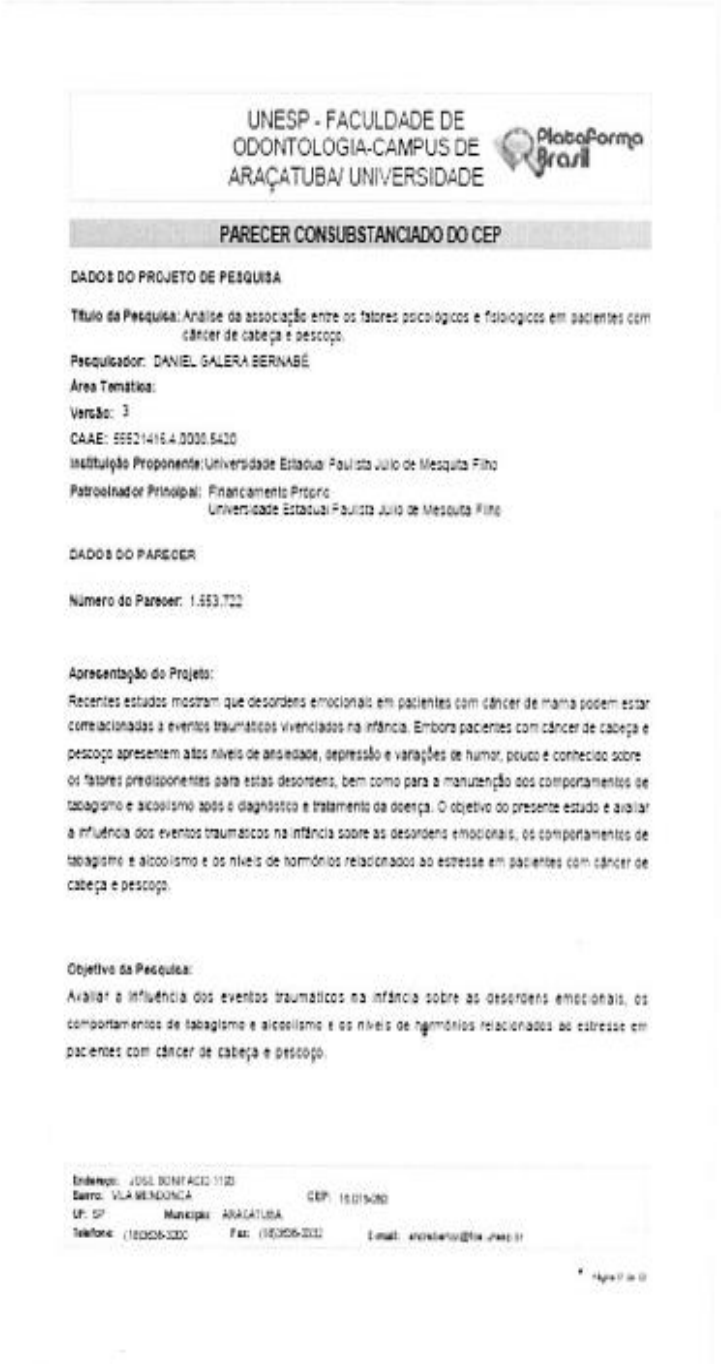
ANEXO A – Comitê de Ética em Pesquisa



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Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Análise da associação entre os fatores psicológicos e fisiológicos em pacientes com câncer de cabeça e pescoço.

Pesquisador: DANIEL GALERA BERNABÉ

Área Temática:

Versão: 3

CAAE: 55521416.4.0000.5420

Instituição Proponente: Universidade Estadual Paulista Júlio de Mesquita Filho

Patrocinador Principal: Financiamento Próprio
Universidade Estadual Paulista Júlio de Mesquita Filho

DADOS DO PARECER

Número do Parecer: 1.553.722

Apresentação do Projeto:

Recentes estudos mostram que desordens emocionais em pacientes com câncer de mama podem estar correlacionadas a eventos traumáticos vivenciados na infância. Embora pacientes com câncer de cabeça e pescoço apresentem altos níveis de ansiedade, depressão e variações de humor, pouco é conhecido sobre os fatores predisponentes para estas desordens, bem como para a manutenção dos comportamentos de tabagismo e alcoolismo após o diagnóstico e tratamento da doença. O objetivo do presente estudo é avaliar a influência dos eventos traumáticos na infância sobre as desordens emocionais, os comportamentos de tabagismo e alcoolismo e os níveis de hormônios relacionados ao estresse em pacientes com câncer de cabeça e pescoço.

Objetivo da Pesquisa:

Avaliar a influência dos eventos traumáticos na infância sobre as desordens emocionais, os comportamentos de tabagismo e alcoolismo e os níveis de hormônios relacionados ao estresse em pacientes com câncer de cabeça e pescoço.

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Plataforma Brasil

Continuação do Parecer: 1.852.702

Avaliação dos Riscos e Benefícios:

Riscos:

Este estudo oferece riscos mínimos aos seus participantes, pois suas metodologias são: coletas de sangue e saliva cujas técnicas são amplamente conhecidas e aplicadas em laboratórios de diagnóstico. Neste estudo a coleta de sangue será realizada por um profissional especializado da área de enfermagem. Os testes psicológicos que serão utilizados são reconhecidos mundialmente e validados na população brasileira e estes serão aplicados por um profissional da área de psicologia.

Benefícios:

As avaliações dos questionários psicológicos serão realizadas por um profissional da área de psicologia que oferecerá suporte psicológico ao paciente caso aja necessidade. A pesquisa favorece o processo de percepção de fatores inconscientes que possam influenciar no modo de viver do indivíduo e de como estes fatores podem interferir na própria doença. Além disso, será oferecido aos grupos controles uma avaliação clínica intraoral com o objetivo de detectar lesões bucais, com isso favorecendo o diagnóstico precoce de possíveis lesões benignas e malignas.

Comentários e Considerações sobre a Pesquisa:

A pesquisa apresenta-se bem estruturada e com objetivos bem definidos.

Considerações sobre os Termos de apresentação obrigatória:

Os termos de apresentação obrigatória foram devidamente apresentados.

Recomendações:

Não há.

Conclusões ou Pendências e Lista de Inadequações:

Propõe-se a aprovação do projeto.

Considerações Finais a critério do CEP:

Salientamos que, de acordo com a Resolução 466 CNS, de 12/12/2012 (Item X, seção X.1., art. 3)

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Plataforma Brasil

Continuação do Parecer: 1.653.722

item b, e, título XI, seção XI.2., item d), há necessidade de apresentação de relatórios semestrais, devendo o primeiro relatório ser enviado até 01/01/2017.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_674460.pdf	22/07/2016 10:29:41		Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_DANIEL_BERNABE_2016.pdf	22/07/2016 09:48:19	Bruna Amelia Moreira Barafim da Silva	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_de_Pesquisa_2016.pdf	22/07/2016 09:47:44	Bruna Amelia Moreira Barafim da Silva	Aceito
Outros	Anexo_Projeto_de_Pesquisa_Daniel_Bernabe_2016.pdf	17/03/2016 10:31:32	DANIEL GALERA BERNABÉ	Aceito
Folha de Rosto	Assinatura_pesquisador_responsave.pdf	22/12/2015 16:47:27	Bruna Amelia Moreira Barafim da Silva	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

ARAÇATUBA, 25 de julho de 2016

Assinado por:
André Pinheiro de Magalhães Bertoz
(Coordenador)

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ANEXO B – Normas para publicação no periódico Head & Neck

Journal: Head & Neck

http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)10970347/homepage/ForAuthors.html