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Relationship between anemia and oral cancer: a case-control study

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Abstract: The aim of this study was to investigate the occurrence, type and severity of anemia at the time of diagnosis of oral cancer, and its potential association with the degree of tumor cell differentiation. This case-control study used 366 medical records of patients treated at two referral centers for oral cancer diagnosis, specifically: cases (n=70) with a histopathological diagnosis of oral squamous cell carcinoma (OSCC) of the oral cavity, and controls (n=296) with benign oral lesions. Sociodemographic, behavioral, and clinical variables of both groups, as well as complete blood count values, were analyzed by descriptive statistics and crude/adjusted logistic regression. Anemia was detected in 15.7% of the cases and 11.8% of the controls. The presence of anemia had an OR=1.64 (odds ratio) (95%CI 0.54–5.00) for OSCC, with no significantly statistical association. Normocytic anemia was the most prevalent form of anemia when oral cancer was diagnosed (91.4% of the controls and 72.7% of the cases), and moderate to severely low hemoglobin levels were associated with OSCC diagnosis (OR 6.49; 95%CI 1.18–35.24), albeit data on hematological examinations were missing.

Keywords: Anemia; Hemoglobins; Mouth Neoplasms; Diagnosis; Case-Control Studies.

Introduction

Oral cancer is the fifth most common malignant neoplasm worldwide, and accounts for the majority of head and neck cancers.[1] According to recent publications, its worldwide incidence ranges from 1.3 to 3 cases per 100,000 person/year among women, and 1.8 to 9.3 per 100,000 person/year among men.[2,3] In Brazil, the National Cancer Institute (INCA) estimates for 2020 have predicted an absolute number of 13,240 new cases of oral cancer among men, and 4,980 among women, with an incidence of 9.2 to 10.7 cases per 100,000 person/year for men and 2.6 to 3.7 per 100,000 person/year for women,[4] thus rendering it a public health problem.

Oral squamous cell carcinoma (OSCC) is the most common type of oral cancer.[5] Although the risk factors for most patients are smoking and alcohol consumption,[6] excessive and cumulative sun exposure is also a potential risk factor for the development of lip cancer.[7] In addition to these hazards, genetic, hereditary and occupational factors, HPV infections, and consumption of some types of food, such as processed meats, are

also described in the literature, and associated with an increased risk of developing OSCC.[8,9,10]

OSCCs are classified microscopically into moderately or poorly differentiated and undifferentiated carcinomas, based on the differentiation of neoplastic cells. Although different factors are investigated,[11] the degree of cell differentiation is one of the most widely used criteria to predict prognosis of the disease.[12] Well-differentiated OSCCs generally show a tendency to metastasize into regional lymph nodes after invading connective, muscle or bone tissue. On the other hand, poorly differentiated OSCCs are biologically more aggressive, with a tendency to progress to regional metastases at an early stage of the disease, and with a greater risk of developing distant metastases.[13]

When analyzing the possible predictive factors that impact the prognosis and quality of life of patients with OSCC, anemia stands out as being associated with a lower response to antineoplastic therapy and reduced survival rates.[14] It is widely accepted that anemia causes resistance to radiotherapy, because hemoglobin (Hb) levels play a key role in tumor oxygenation. The low Hb characteristic of anemia is one of the causes of tumor hypoxia, and may lead to decreased tumor radiosensitivity. The radiation doses required to destroy hypoxic cells are estimated to be two- to threefold higher than those required to destroy well-oxygenated malignant cells. During prolonged hypoxia, tumor cells may become resistant to apoptosis, owing to the stimulation of genomic changes that transform into a more aggressive and infiltrative phenotype.[15]

Studies evaluating the relationship between anemia and OSCC have shown that the presence of anemia is associated with a poor prognosis, which increases the risk of mortality by decreasing control of the disease and overall survival.[16,17] Other studies have found that anemia is caused by the antineoplastic treatment itself;[18,19] however, it has been reported that many patients are already anemic when starting the treatment.[16] This may be due to chronic inflammation secondary to the activation of the immune system, leading to the release of cytokines and proteins of the acute phase, especially in advanced stages of cancer.[18] The severity of anemia is directly related to the size of the tumor, and the histological degree of cell differentiation.[17]

An analysis of studies published in recent years led us to observe that most studies assess the presence of anemia during[20] and after cancer treatment,[19] and focus on the prognosis and survival of patients with cancer in the region of the head and neck,[21,22,23] whereas few studies evaluate cancer solely in the oral cavity.[16,17] Contrastingly, the presence of anemia is rarely reported when OSCC is diagnosed. Therefore, the aim of this study was to investigate the frequency, type and severity of anemia at the time of diagnosis of oral cancer, and to test the hypothesis that its presence is related to the diagnosis of OSCC, and that it is associated with the degree of tumor cell differentiation.

Methodology

This was a case-control study based on secondary data from medical records. It was approved by the research ethics committee (CEP nº 2,751,612) and conducted in accordance with National Health Council Resolution 466/12. Medical records were anonymized and identified by numeric codes to preserve the participants' confidentiality.

Population, eligibility criteria, and sample size calculation

The sample was drawn from medical records of patients treated from March 2006 to June 2019 at the Stomatology and Head and Neck Surgery Departments of a university hospital in Canoas, Rio Grande do Sul, Brazil.

Patients with a histopathological diagnosis of OSCC, which related the anatomical sites of the tongue, oral floor, lip, gums, retromolar region and palate, with blood count values prior to the biopsy procedure, are described in the medical records. Records of patients who had a history of cancer elsewhere, metastasis, recurrence of oral cancer, previous antineoplastic treatment, and/or who were under anemia treatment were excluded.

Patients with a histopathological diagnosis of lesions, or benign oral neoplasms, with complete blood count values prior to the biopsy procedure

for diagnosis, are described in the medical records. Records with cases of potentially malignant lesions, history of malignancy, antineoplastic treatment and/or treatment of anemia were also excluded.

The sample size was calculated to estimate an odds ratio of 2.5, with a 5% significance level and 10% beta error (90% power). This effect size was based on a previous study investigating the increased risk of cancer in patients with iron deficiency anemia (standardized incident ratio [SIR] = 2.15). [24] In addition, a 1:4 ratio of case to control was established, based on a 9% to 21% prevalence of anemia found in a Brazilian study [25]. Therefore, the final sample size was estimated at 344 controls and 86 cases.

Data collection

A trained investigator searched all the papers and digital files of both the head and the neck surgery departments of the university hospital, and selected those surgeries that met the eligibility criteria. The same investigator then extracted data using a standardized form divided into three domains, according to the following variables of interest: a) demographic factors (sex, age, race); b) behavioral factors (smoking and alcohol intake, and their duration); and c) complete blood count values. In the case group, the clinical characteristics of the OSCC were also recorded, specifically its location, according to tumor origin codes adapted from the International Classification of Diseases for Oncology [ICD-O],[26] and its cell differentiation grade, as described in the pathology reports, according to the tumor classification.[26]

For analytical purposes, cell differentiation was categorized dichotomously into the following grades: a) well to moderately differentiated, or b) poorly differentiated to undifferentiated. Cases in which the histological grade was unspecified or not described were excluded from analysis. Complete blood counts were analyzed for red blood cells (erythrocyte count), Hb and hematocrit (Hct), to investigate the presence, type (normocytic, microcytic, or macrocytic), and severity (mild, moderate, or severe) of anemia, according to the established reference ranges.[27]

The diagnosis of anemia was based on the World Health Organization standardized cut-off values[19] of Hb < 13 g/dL and Hct < 39% for men, and Hb < 12 g/dL and Hct < 36% for women. The type of anemia was classified by mean corpuscular volume (MCV) as microcytic (MCV < 80 fL), normocytic (MCV = 80–100 fL), or macrocytic (MCV >100 fL).[27] Severity of anemia was classified according to the Hb level as mild (11–11.9 g/dL for women, 11–12.9 g/dL for men) or moderate to severe (< 10.9 g/dL). For analysis and comparison purposes, Hb values within the normal range were classified as "no anemia."

Data analysis

The data were analyzed using descriptive statistics (absolute and relative frequencies of qualitative variables). A comparison of the characteristics between case and control group participants was performed using the chi-square test with or without ordinal trend (age range and duration of alcohol consumption and smoking). The low sample size determined the use of Fisher's exact test to test for the association of demographic variables, behavioral variables, and complete blood count values with tumor differentiation grade. The statistical significance level was set at 5%. The covariates associated with anemia and OSCC were analyzed, and the results were expressed as crude odds ratios (OR) using simple unconditional logistic regression, and adjusted ORs using unconditional multiple logistic regression, with a 95% confidence interval (CI). The final adjusted model included all potential confounding variables based on previous studies, regardless of statistical significance, but arising from bivariate collinearity between anemia and hemoglobin level. One adjusted model was calculated for each confounding variable. All analyses were performed using Stata version 13.1.

Data availability

The data investigated is not available to be shared publicly outside the university hospital, since the authors are not allowed to distribute it. However, analytical methods are available upon request made to the corresponding author.

Results

The total sample comprised 366 medical records: 70 cases (19.1%) and 296 controls (80.9%). This

sample size had a power of 84% for detecting the supposed OR described in previous studies. A comparison of demographic characteristics, behavioral variables, and complete blood count values between cases and controls is shown in Table 1. Most cases were white (88.5%), men (75.7%), aged 40 to 79 years (90%). Conversely, most controls were women (60.8%), in the 40-to-79-year age range (82.4%), and white (83.4%). Both the frequency of smokers (82.9%) and the reported alcohol intake rate (34.1%) were higher among the cases, with a duration exceeding 20 years for the vast majority (74.3%).

Anemia was found in 46 participants: 11 cases (15.7%) and 35 controls (11.8%), with no significant intergroup difference (p = 0.38). However, there was a statistically significant difference in the distribution of hemoglobin levels (p = 0.02) and types of anemia (p = 0.02) between cases and controls, in that mild was more frequent than moderate/severe anemia degree, and normocytic was more frequent than microcytic or macrocytic anemia types.

Table 1. Distribution of demographic, behavioral, and clinical variables in the case and control groups.

Variable	Total		Control		Case		p-value
	%	(n)	%	(n)	%	(n)	
	100	-366	100	-296	100	-70	
Sex							
Female	53.8	-197	60.8	-180	24.3	-17	< 0.01
Male	46.2	-169	39.2	-116	75.7	-53	
Age range*							
20–39	13.9	-46	15.7	-41	7.1	-5	0.03
40–59	41.4	-137	42.2	-110	38.6	-27	
60–79	42.6	-141	40.2	-105	51.4	-36	
> 80	2.1	-7	1.9	-5	2.9	-2	
Race*							
White	84.5	-212	83.4	-166	88.5	-46	0.37
Black/Brown	15.5	-39	16.6	-33	11.5	-6	
Smoking							
Never	62.8	-230	73.7	-218	17.1	-12	< 0.01
Up to 20 years	7.9	-29	7.8	-23	8.6	-6	
> 20 years	29.2	-107	18.6	-55	74.3	-52	
Alcohol intake*							
Never	88.2	-268	91.9	-239	65.9	-29	< 0.01
Up to 20 years	4.0	-12	3.5	-9	6.8	-3	
> 20 years	7.9	-24	4.6	-12	27.3	-12	
Anemia							
No	87.4	-320	88.2	-261	84.3	-59	0.38
Yes	12.6	-46	11.8	-35	15.7	-11	
Hemoglobin							
Normal	84.4	-309	86.0	-260	75.5	-49	0.02
Low (mild)	11.9	-43	11.3	-34	15.1	-9	
Low (moderate/severe)	3.8	-14	2.7	-8	9.4	-6	
Anemia type*							
Normocytic	87.0	-40	91.4	-32	72.7	-8	0.02
Microcytic	6.5	-3	8.6	-3	0.0	0	
Macrocytic	6.5	-3	0.0	0	27.3	-3	

*Sample size with missing data due to incomplete record-related information.

The degree of cellular differentiation of the OSCC could be identified in 31 cases, because the classification was described in the histopathological report. These data were categorized dichotomously, that is, in degrees of differentiation from moderate to very low (n = 19) and from little differentiated to undifferentiated (n = 12). The male sex presented the highest frequency of cases for degree of cellular differentiation: both well to moderate (94.7%) and poorly differentiated to undifferentiated (75%). Among the cases with a degree of cellular differentiation between good and moderate, 75% had anemia of the normocytic type at the time of diagnosis, whereas those with a degree of little differentiated to undifferentiated had more cases of anemia of the macrocytic type (66.7%). However, the degree of cell differentiation of the tumor was not associated with other variables, such as tumor size (p = 0.49), smoking (p = 0.90), alcohol consumption (p = 0.26), or presence (p = 0.57), type (p = 0.37) or severity of anemia (p = 0.87) at the time of diagnosis.

ORs and 95%CIs in crude and adjusted models were analyzed in relation to the variables of sex, age range, smoking, alcohol intake, and presence of anemia. Owing to the collinearity of the variables – anemia (model 1) and hemoglobin level (model 2) – two adjusted models were needed to avoid increasing the standard error. Men were four times more likely to be diagnosed with OSCC (OR 4.84; 95%CI 2.64–8.76) than women, thus maintaining the statistical significance in adjusted models 1 and 2, respectively (OR 4.65; 95%CI 2.02–10.70; OR 4.23; 95%CI 1.72-10.38). Among 20-plus-year smokers, the odds were 17 times higher (OR 17.18; 95%CI 8.58–34.38), thus also maintaining the statistically significant difference after adjustment for models 1 and 2 (OR 14.56; 95%CI 5.91-35.90; OR 11.56 95% IC 4.41–30.29). The presence of anemia itself was not associated with the diagnosed presence of OSCC (OR 1.39; 95%CI 0.67–2.90) and remained with no statistically significant difference, even after application of adjusted model 2 (OR 1.64; 95%CI 0.54–5.00). On the other hand, moderate to severely low Hb levels were associated with the diagnosed presence of OSCC both in the raw model (OR 3.94; 95%IC 1.23-12.64) and in adjusted model 1 (OR 6.46; 95%CI 1.18–35.24) (Table 2).

Discussion

In this study, anemia was associated with an increase in OSCC; however, it was not statistically significant, thus refuting our hypothesis. The instances of anemia observed in the case group may have been attributed to the disease itself, given that normocytic anemia is commonly associated with the inflammatory process of chronic diseases such as cancer.[29,30] Among the group of controls, who also had a high prevalence of normocytic anemia, this finding of disease-related anemia was probably due to the presence of other chronic comorbidities.

No relationship was found between Hb levels and grade of OSCC differentiation; however, this analysis was limited to eligible cases for which a description of histological grade was available in the medical record, a limitation which undoubtedly interfered with our findings. Another study[17] found that Hb and Hct levels gradually decreased as size and cellular differentiation of malignant tumors increased. This is a result of the hemolysis products caused by chronic erythrocyte destruction. Our study used the degree of cell differentiation as the criterion for histopathological gradation of the tumor, as recommended by the World Health Organization,[31] and according to the availability of the medical records of the patients studied. In contrast, some recent studies have suggested new histopathological systems of classification, such as Tumor Budding and Cell Nest Size, recently identified as histomorphometric factors of high prognostic power in biopsy specimens of squamous cell carcinoma in several anatomical sites.[32]

Our findings corroborate those of previous studies, namely, that patients with cancer may already be anemic even before they start their radiotherapy and/or chemotherapy treatment,[16] and that anemia may be a predictor of poorer response to treatment,[33] owing to lower radiosensitivity caused largely by tumor hypoxia.[34] Anemia in head and neck cancer patients is associated with poorer prognosis and increased mortality,[16,19,20,22] and is often neglected before and during cancer treatment.[35] Therefore, the presence of anemia at the time of diagnosis of oral cancer may place these patients at greater risk of poor response to antineoplastic therapy.

Table 2. Odds ratios (95%CI), crude and adjusted for associations between oral squamous cell carcinoma (OSCC) and demographic variables, behavioral variables, and anemia.

Variable	Crude		Adjusted* 1		Adjusted* 2	
	OR	IC95%	OR	IC95%	OR	IC95%
Sex						
Female	1		1		1	
Male	4.84	2.67–8.76	4.65	2.02–10.70	4.23	1.72–10.38
Age range						
20–39	1		1		1	
40–59	2.01	0.73–5.58	1.06	0.27–4.20	0.97	0.24–4.00
60–79	2.81	1.03–7.66	1.38	0.37–5.25	1.16	0.29–4.67
> 80	3.28	0.50–21.59	3.75	0.27–52.32	4.06	0.28–57.92
Race						
White	1.		1		1	
Black/Brown	0.66	0.26–1.66	0.32	0.10–1.02	0.31	0.09–1.06
Smoking						
Never	1		1		1	
Up to 20 years	4.74	1.63–13.82	2.54	0.64–10.06	2.54	0.62–10.44
> 20 years	17.18	8.58–34.38	14.56	5.91–35.90	11.56	4.41–30.29
Alcohol intake						
Never	1					
Up to 20 years	2.75	0.70–10.73				
> 20 years	8.24	3.39–20.03				
Anemia						
No	1		1			
Yes	1.39	0.67–2.90	1.64	0.54–5.00		
Hemoglobin						
Normal	1				1	
Low (mild)	1.53	0.66–3.54			2.05	0.59–7.13
Low (moderate/severe)	3.94	1.23–12.64			6.46	1.18–35.24
Goodness of fit test (Hosmer-Lemeshow)			p = 0.20		p = 0.61	
Accuracy			83.9%		85.6%	
Pseudo-R^2			30.5%		26.6%	

*Anemia and hemoglobin are collinear, and different models were built for each one. Alcohol was excluded from the adjusted model due to multicollinearity.

Iron-deficiency anemia is considered a risk factor for the development of various cancers, with a standardized incidence rate (SIR) of 1.33 (95%CI 1.01–1.72). [25,36] However, no cases of this type of anemia were identified in our sample. Nonetheless, we must take into account that most studies do not classify or specify the type of anemia; this may constitute a confounding factor, and fail to represent the actual distribution of types of anemia in patients with oral cancer.

Nonetheless, Hb levels were associated with a sixfold increase in the odds of OSCC diagnosis. Therefore, this important finding warrants a more in-depth investigation to offset the limitations of the current study, such as small sample size compared to the number of eligible cases. The reduction in the hemoglobin level may reflect the presence of chronic inflammation due to tumor progression, given that persistent inflammation plays an important role in oral carcinogenesis. This is because of the release of pro-inflammatory cytokines as a tumor necrosis factor, and because the immune response is decreased due to immunosuppressive cytokines, such as interleukins (IL-6). Our hypothesis is that the

greater chance of diagnosing OSCC among patients with moderate to severe Hb levels may be mediated by these inflammatory biomarkers.[37]

Demographic and behavioral variables were associated with OSCC, as corroborated by other studies.[32,38] Although there is an upward trend in OSCC among women, OSCC levels are still higher among males.[5,32] The higher prevalence of females in the control group could be attributed to women being more concerned about health and seeking care[39]. This could explain the higher number of female patients using our service. Our difficulties in matching four controls for each case led to our having to opt to control for possible confounding factors in the analyses. These included demographic (sex and age) and behavioral variables. In addition, we found that men were significantly more likely to be diagnosed with OSCC; the risk was 8- to 14-fold greater among those who consumed alcohol, and who had smoked for more than 20 years, respectively, compared with patients not diagnosed with OSCC. These differences were observed even in the adjusted model.

The limitations of the present study must also be taken into account, including the use of retrospective data (information from medical records), a method inherent to the study design itself. This led to loss of information and missing data for some variables of interest, most notably the histological grade of OSCC. Another limiting factor for data analysis was the difficulty in reaching the calculated sample size, especially because of the eligibility criteria for the participants in the case group. However, the ratio of 4:1 controls for each case allowed the control-to-case OR to be calculated.

Nonetheless, this study has several strengths. First, it contributes to the limited evidence about anemia at the time of the diagnosis or prior to onset of treatment. To the best of our knowledge, this was the first study in a Brazilian population that not only investigated the frequency of anemia at the time of diagnosis, but also assessed the type and severity of the anemia.[16,33,40] Second, it used standardized diagnostic and classification criteria, such as the Hb cut-offs defined by the World Health Organization,[28] as well as hematocrit, which is a clinical indicator of the red blood cell count, and is directly related to the Hb level, and to the oxygen-carrying capacity of blood.[40]

Lastly, further studies are needed, especially prospective and population-based ones, with larger samples to help better elucidate the role of anemia as a potential predictor of oral cancer development, as regards its response to antineoplastic treatment, and its possible role in patient survival and impact on the patient's quality of life.

Conclusion

Our sample showed a non-significant association between the diagnosed presence of OSCC and anemia. Normocytic anemia was the most prevalent form of anemia at the time of oral cancer diagnosis, and moderate to severely low hemoglobin levels were associated with the diagnosed presence of OSCC, albeit data were missing on hematological examinations.

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