Diabetes Mellitus as a risk for oral cancer: A Case-Control Study

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KEYWORDS

Alcohol; chewing tobacco; Diabetes Mellitus; oral cancer and tobacco

ABSTRACT

Introduction: Diabetic patients had an increased risk of cancer at some HNC subsites like oral cancer, while in other studies this risk was decreased. The association of diabetes mellitus (DM) with head and neck cancers (HNC) is still controversial. So, the present study aims to assess the association of diabetes mellitus, and oral cancer and the role of habits in association with DM in the progression of oral cancer. **Materials and methods:** This study was undertaken at the Karpaga Vinayaga Institute of Dental Sciences, Tamilnadu. The study includes 2 main groups, which are 300 Oral cancer patients and a Control group that includes 300 age and gender-matched patients assessed with habits and Diabetes. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression. **Results:** Out of 600 subjects increased risk of diabetes in oral cancer was observed. On comparison between oral cancer, diabetes and habits in study group and control group, an increased risk was observed among males (aOR = 1.00, 95% CI = 1.000 to 1.312), alcoholics (aOR = 2.317, 95% CI = 1.181 to 2.557), smokers (aOR = 2.938, 95% CI = 0.860to 4.374), and chewing (aOR = 2.532, 95% CI = 1.100 to 2.608). **Conclusion: T**he present population-based study results suggest a direct association between diabetes and oral cancer.

INTRODUCTION:

Cancer is the 2nd leading cause of death worldwide, accounting for approximately an estimated 9.6 million deaths in 2018 (WHO, 2018). Oral cancer which is a subtype of head and neck cancer is any cancerous tissue growth located in the oral cavity.[1] Oral cancer accounts for approximately 4-5% of all cancers and is the sixth most common cancer.[2] Oral cancer is one of the most prevalent malignant neoplasms of the head and neck region. It accounts for 354,864 new cancer cases and 177,384 deaths per year worldwide, with higher rates in developing countries.[3]

Diabetes Mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia caused by a defect in insulin secretion, insulin function, or both. Globally, it was estimated that in 2017, 451 million people aged 18–99 years had diabetes and these figures are expected to increase to 693 million by 2045.[4]

Smoking and alcohol use are the two main risk factors linked to Head and Neck Cancers (especially oral cancers), and these two variables might interact to raise the risk of head and neck cancers. Poor oral health, diet, genetics, a low body mass index (BMI), and job characteristics are additional risk factors.[5] Many epidemiological reports have shown that diabetes is positively associated with several types of cancers including breast, colorectal, endometrial, liver, and pancreatic cancers. Studies have shown a strong correlation between diabetes mellitus and carcinogenesis and the most evident correlation is reported with type 2 diabetes mellitus.[6,7] Additionally, the link of DM with malignant tumors has been repetitively described. Patients with type 2 DM are at a greater risk of both developing and succumbing to

cancer.[8] Oxidative stress and DNA damage secondary to hyperglycemia, activation of insulin receptors and insulin-like growth factor receptors via hyperinsulinemia resulting in accelerated cell cycle progression, or chronic inflammation have been discussed as possible explanations for the linkage between DM and cancer.[9] The proliferation of cancer cells which is induced by hyperglycemia/diabetes occurs indirectly by mediating the following processes (1) insulin and insulin-like growth factor 1 (IGF-1), (2) secretion of leptin/adiponectin, (3) inflammatory responses, (4) production of reactive oxygen species (ROS; oxidative stress) and (5) immune abnormalities (platelet activation). In addition to a direct correlation between impaired glucose tolerance/diabetes and the initiation of cancer, proliferation, and invasiveness may occur due to hyperglycemia.[10]

Both diabetes and oral cancer have a dramatic detrimental effect on both the mortality rate and the quality of life, [11] and the simultaneous rise in incidence rates of both diseases has spurred the research community to search for a possible correlation in terms of pathophysiological pathways. This study sought to advance the topic by testing the hypothesis that diabetes mellitus may have an independent effect on the likelihood of oral cancer risk. Hence the study aimed to determine whether there is an association between diabetes mellitus and oral cancer risk in a hospital-based case-control study.

MATERIALS AND METHODS:

A hospital-based case-control study was conducted with patients recruited from the Karpaga Vinayaga Institute of Dental Sciences from September 2015 to January 2022 in Chengalpattu district, India. All patients signed informed consent and ethical clearance was given by the Institutional ethics committee. The inclusion criteria were: (a) histologically confirmed primary oral cancer; squamous cell carcinoma of the oral cavity (b) age between 20 and 80 years. Exclusion criteria included: (a) Participants who did not consent to participate in the study; (b) Patients confirmed with oropharynx or head and neck cancers histologically.

SELECTION OF CASES AND CONTROLS:

In this case-control study, a group of patients with OC was compared to a group of patients who did not have OC. The database collected from patient records contains the cancer site, age, gender, area of residence, habits (tobacco use, smoking, alcohol), and the presence of diabetes mellitus.

The case group consisted of 300 patients with a histologically confirmed OSCC diagnosis. In contrast, the control group consisted of the other 300 patients who did not have OC in their medical history. Patients were selected regardless of the presence of bad habits (smoking and alcohol consumption). In the case group, patients were selected with a histologically confirmed diagnosis of oral SCC (in the upper lip, lower lip, buccal, gingiva, tongue, sublingual region, or palate). Patients enrolled in the control group were the eligible family members and caregivers. Participants in the control and case groups were frequency-matched by age.

Participants who reported they were diabetic at the interview or, had a diagnosis of DM in medical records. Diabetes was validated with preoperative glucose level by categorizing FPG into 2 groups according to the diagnostic criteria of the American Diabetes Association (2014): no, FPG □126 mg/dL; yes, FPG □126 mg/dL, insulin shots, antidiabetic medication, and/or diagnosis by physician.[12] Individuals who presented with an already established diagnosis of type 1 or type 2 DM were accordingly listed as patients with DM. We defined impaired fasting glycemia (IFG) as fasting blood glucose levels between 6.1 and 6.9 mmol/l.

Data collection:

All participant data, including demographics like gender and age (continuous), as well as health-related behavioral factors like alcohol consumption, smoking, and medical history of systemic disorders (diabetes), were gathered in person by trained personnel. Serum laboratory testing was used to determine preoperative fasting plasma glucose (FPG).

Statistical analysis:

All the findings were entered in Microsoft Excel using SPSS 20.0 software. The characteristics of the variables were derived with mean ± SD values for the continuous variable (age) and

frequency distributions for the categorical variables. Odds ratios (OR) and 95% CI were estimated using conditional logistic regression.

Results:

This hospital case-control study consisted of 600 participants: 300 OSCC cases (199 (66%) male and 101 (34%) female; mean age, 63.8 years) and 300 controls (235 (78%) male and 65 (22%) female; mean age, 64.4 years). As compared with controls, cases included patients with fewer alcohol drinkers, chewers, and more patients with diabetes. (Table 1)

Distribution of Oral cancer according to gender

Out of 600 subjects, a direct relation between DM with oral cancer was observed [P=0.021]. The risk was statistically significant when all individuals (OR: 2.55 and 95% CI: 1.221 - 5.708) were analyzed. Compared with patients having normal status, males having oral cancer were 1.6 times more likely to have diabetes (OR: 1.60; and 95%CI: 1.04 - 2.46). (Table 2).

Distribution of Oral cancer according to habits

On comparison between oral cancer, diabetes, and habits in the case group and control group, increased risk was observed with smokers (OR: 3.538 and 95%CI: 1.726 -7.251) and chewers (OR: 1.131 and 95% CI: 1.085 – 1.869) and alcoholics (OR: 1.770 and 95% C.I:1.305 – 1.940) (Table 3).

Association between Diabetes and Oral cancer

Compared with patients without diabetes, those with diabetes were 3.5 times more likely to have OSCC (aOR = 2.515, 95% CI = 1.221 to 5.180), thereby showing a significantly increased risk and direct relationship (trend, P = 0.003; Table 3, model 1). The findings encompassing diabetes also showed a significant association with Oral cancer (bOR = 2.518, 95% CI = 1.227 to 5.164; Table 3, model 2 adjusted for gender). There was an effect modification by gender, smoking, alcohol, and chewing on the association of diabetes with Oral cancer. The link was more highlighted among males (aOR = 1.00, 95% CI = 1.000 to 1.312), alcoholics (aOR = 2.317, 95% CI = 1.181 to 2.557), smokers (aOR = 2.938, 95% CI = 0.860to 4.374), and chewing (aOR = 2.532, 95% CI = 1.100 to 2.608) and showed an increased risk for oral cancer. The Odds ratio value is reduced after adjusting for gender (Model 2). [Table 4]

Discussion:

In this present study, 300 oral cancer patients included in the study group were all priorly histopathologically diagnosed cases. 300 age-matched controls with deleterious habits and without any premalignant lesions were recruited from the Department of Oral and Maxilla Facial Surgery in our Institute.

In the present study out of 300 cases of carcinoma comparing all subsites of oral cancer, tongue 139 (46.3%) and buccal mucosa 94 (31.3%) combining both left and right side were found to be with higher prevalence and least prevalence was seen with lip 23 (7.7%) which was following the previous studies. [13,14] Among 300 oral cancer patients, 147 (49%) patients had smoked tobacco and 112 (37.3%) had chewing tobacco in the 300-control group with habits 129 (43%) had a smoking habit, and 130 (43.4%) had chewing tobacco habit which is in accordance with the done by Jain et al.[15]

In the present population-based study, out of 300 oral cancer patients, 212 (70.6%) were diabetic and 88 (29.3%) were non-diabetic and in 300 controls with habits, 179 (59.6%) were diabetic and 121 (40.4%) were diabetic. Our data showed that the prevalence of diabetes was high in oral cancer which signifies a positive association between DM and oral cancer like previous studies. [16,17] Our results confirmed previous studies [17] showing the positive association of diabetes with oral cancer and those with diabetes are 2.5 times more likely than those without diabetes to have oral cancer, after controlling for various confounders, stating diabetes has a synergistic effect on the development of oral cancer.

The novelties of this study as compared with previous reports are as follows. First, hospital cases were based on patients with oral cancer, while the controls were from the population of

family and caregivers, which reduced the bias associated with errors resulting from hospital controls. Second, despite the rarity among cancers, enough cases were included, which reduced the uncertainty due to small numbers. Third, controls were selected by matching well-known risk factors, such as gender, to cases that adjusted the influence of these factors on the association. Fourth, the history of diabetes was confirmed with laboratory tests, which reduced information bias due to the misinterpretation of diabetes. Fifth, definitive confounders—including gender, alcohol intake, smoking, and chewing—were added to the model for the adjustments.

There are several limitations to this study. First, there is an inherent selection bias for controls in case-control study designs. However, because oral cancer is an uncommon disease among other cancers, it is the best study design for cancer research. Second, there was little data on other possible risk factors, like dietary changes, precancerous lesions, and medications. These constraints can cause the correlation to be overestimated.

Conclusion:

Overall, our data showed that diabetes was independently associated with OSCC. Thus, diabetes could be a risk factor for oral cancer and its progress. Moreover, the high-risk groups were males. Prevention and control of diabetes could thus serve as preventive care for oral cancer, which could be of great clinical relevance. Hence, it is speculated that the risk of oral cancer could be modulated through the control of diabetes.

Table 1: Characteristics of the Study Participants by Case/Control Status

a Variables		Cases (N=300)		Controls (N=300)	
		N	%	N	%
Sex	Male	199	66	235	78
	Female	101	34	65	22
Smoking Status	Smokers	147	49	129	43
	Non-Smokers	153	51	171	57
Tobacco Chewing	Chewers	112	37.3	130	43.3
	Non-Chewers	188	62.7	170	56.7
Alcohol Status	Alcoholic	106	35.3	110	36.7
	Non-Alcoholic	194	64.7	190	63.3
Presence Of DM	Diabetic	212	70.6	179	59.6
	Non-Diabetic	88	29.3	121	40.3
Site Of Oral Cancer	Tongue	139	46.3		
	Buccal Mucosa	94	31.3		
	Alveolus	24	8		
	Lip	23	7.7		
	The floor of the mouth	20	6.7		

		Group		P-Value	Odds Ratio	95% CI.For Odds Ratio	
		Case Group n(%)	Control Group n(%)			Lower	Upper
All Individuals	Diabetic	212 (70.6)	179 (59.6)	0.021*	2.550	1.221	5.180
	Non-Diabetic	88 (29.3)	121 (40.3)				
Female	Diabetic	85 (63.4)	49 (36.6)	0.165	1.735	.798	3.773
	Non-Diabetic	16 (50.0)	16 (50.0)				
Male	Diabetic	161 (46)	272 (54)	0.029*	1.609	1.049	2.468
	Non-Diabetic	38 (37.6)	63 (62.4)				

Table 2. Odds Ratios (OR) and Confidence Intervals (CI) of the Association between Diabetes Mellitus (DM) and Oral Cancer for all Participants and Stratified by Gender

Table 3. Odds Ratios (OR) and Confidence Intervals (CI) of Oral Cancer According to Diabetes Mellitus (DM) by Smoking, Chewing Tobacco, and Alcohol

Variables		Group		P-Value	Odds Ratio	95% C.I. For Odds Ratio	
		Case Group (%)	Control Group (%)			Lower	Upper
Non-Smokers	Diabetic	109 (43.9)	139 (56.1)	0.804	0.940	0.579	1.528
	Non-Diabetic	44 (57.9)	32 (42.1)				
Smokers	Diabetic	137 (62.5)	82 (37.5)	**0.001***	3.538	1.726	7.251
	Non-Diabetic	10 (17.5)	47 (82.5)				
Non-Chewers	Diabetic	173 (58.4)	123 (41.6)	0.205	0.431	0.315	4.493
	Non-Diabetic	15 (24.2)	47 (75.8)				
Chewers	Diabetic	73 (42.6)	98 (57.4)	**0.030***	1.131	1.085	1.869
	Non-Diabetic	39 (54.9)	32 (45.1)				

Non-Alcoholic	Diabetic	151 (55.6)	120 (44.4)	0.105	0.786	0.186	2.688
	Non-Diabetic	43 (38.1)	70 (61.9)				
Alcoholic	Diabetic	95 (48.5)	101 (51.5)	**0.079***	1.770	1.305	1.940
	Non-Diabetic	11 (55.0)	9 (45.0)				

Variables	Adjusted Odds Ratio (95% CI)	
	Model 1[a]	Model 2[b]
Gender		
Female	1	
Male	1.001 (1.000 t0 1.312)	
Alcohol intake No	1	1
Yes	2.317 (1.181 to 2.557)	1.313 (1.178 to 1.549)
Diabetes		
No	1	1
Yes	2.515 (1.221 to 5.180)	2.518 (1.227 to 5.164)
Chewing		
No	1	1
Yes	2.532 (1.100 to 2.608)	1.532 (0.900 to 2.609)
Smoking No	1	1
Yes	2.938 (0.860 to 4.374)	2.508 (0.851 to 4.277)

Table 4. Adjusted Association between Diabetes and Oral Squamous Cell Carcinoma

[a]Model 1: Adjusted association of diabetes by multivariable conditional logistic regression model, conditional on gender, and smoking, alcohol, Chewing.
[b]Model 2: Adjusted association of diabetes by multivariable conditional logistic regression model adjusted for gender, same as Model 1.

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