

RESEARCH ARTICLE

Carcinoma of the Tongue: A Case-control Study on Etiologic Factors and Dental Trauma

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Abstract

Background: Carcinoma of the tongue is the most common intra-oral malignancy in Western countries. Incidence and mortality rates have increased in recent years, and survival has not improved. This study aimed to determine etiologic factors for tongue cancer with age-sex matched case-control data. **Materials and Methods:** 47 patients with carcinoma of the tongue referred to our oral medicine clinic between years 2005-2006 were analyzed and compared with control group data. The medical records, including family history of cancer, dental trauma, and history of abuse of alcohol and tobacco products was recorded for all subjects. Chi square comparison tests and linear regression analysis were performed using the SPSS program for statistics. **Results:** Patient and randomly selected control groups each consisted of 30 male and 17 female subjects with mean ages 53.2 (± 12.6) and 52.6 (± 11.5) years respectively. Smoking and alcohol abuse proportions were significantly higher in the patient group ($p=0.0001$, $p<0.0001$ respectively). Chronic mechanical trauma was observed in 44.7% of the patients and 17.0% of the control group ($p=0.004$). Similarly, family history of cancer of any type (for the first degree relatives) was found to be more common in the patient group ($p=0.009$). On regression analysis, alcohol abuse, family history of cancer, smoking, chronic mechanical traumas appeared as significant etiologic factors ($p=0.0001$). **Conclusions:** We believe that field cancerization may become evident in oral and oropharyngeal mucosa with multiple steps of molecular changes starting from the first sign of dysplasia with chronic exposure to etiological factors. Chronic trauma cases need particular attention to search for very early signs of cancer.

Keywords: Tongue cancer - etiologic factors - dental trauma - field cancerization - dysplasia

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Introduction

Oral squamous cell carcinoma (OSCC) is a malignant epithelial tumor which is the most common intra-oral malignancy in Western countries (Benevenuto et al., 2012). The carcinoma of the tongue represents up to 50% of all cases of OSSC, with the lateral borders and the anterior two thirds the most commonly affected locations (Albuquerque et al., 2012).

The high incidence of tongue cancer in some population groups is thought to be result of cultural habits, such as the chewing of tobacco in South Asia and alcohol use in parts of Western Europe (Pontes et al., 2011). The incidence peaks around sixth to seventh decade of life and especially affects men (Benevenuto et al., 2012). In fact, although the global incidence of OSSC has decreased, the incidence of oral cancer has increased among people less than 40 years of age, a group not normally associated with the consumption of alcohol and tobacco (Albuquerque et al., 2012).

Actually, in this group, the proportion of women with oral tongue squamous cell carcinoma is higher when

compared with the general population (Llewellyn, 2001; Shiboski, 2005).

The known major avoidable risk factors of oral cancer include tobacco, alcohol and many researches are conducted for this theme (Dahlstrom et al., 2008; Allam et al., 2011; Albuquerque et al., 2012). The public health strategies have also been composed on avoiding oral cancer. Though this process is in a meaningful manner, the oral cancer rate has not decreased over the last decade. Furthermore, the second point is there has always been a group of OSSC patients without tobacco and alcohol consumption (Schmidt et al., 2004; Dahlstrom et al., 2008). Especially for the latter, many studies on etiologic factors including HPV 16-18, diet and nutrition, genetics, oral hygiene, dental trauma still continue (Wight et al., 2003; Goldergberg et al., 2004; Sturgis et al., 2004).

If avoiding etiologic factors is taken in consideration as step one, the second important step is early recognition of OSSC. Tumor stage at diagnosis is the most important prognostic marker for OSSC (Massano et al., 2006). Unfortunately, almost half of the oral cancers are diagnosed at advanced stages (stage III or IV), with 5-year

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survival rates ranging from 20-50%, depending on tumor sites (Neville et al., 2002; Warnakulasuriya et al., 2009). The overall diagnostic delay would include the period elapsed since the first symptom or sign until the definitive diagnosis (Gomez et al., 2010).

This study aimed to discuss risk factors of tongue cancer with an age-sex matched control group data as well as diagnostic delay factors.

Materials and Methods

The current analysis included cases only with primary tongue cancers and all controls. Records that belong to 47 cases of carcinoma of the tongue patients who referred to Istanbul University Faculty of Dentistry, Department of Oral and Maxillofacial Surgery clinics from Department of Radiation Oncology or Department of Otorhinolaryngology, Istanbul University Faculty of Medicine were analyzed and compared with 47 age-sex matched cancer-free control group data. The medical records of patient group, including tumor size, location (base of the tongue, mobile tongue, floor of the mouth), node metastasis, grade, recurrence of disease, other primary cancers, delay time until diagnosis, therapy course were noted. Staging of tumors was performed based on pathologic TNM classification according to the American Joint Committee on Cancer (AJCC) cancer system (Edge et al., 2010).

Other recorded data included family history of cancer, dental trauma, dental hygiene and denture status, history of alcohol abuse and tobacco products. Dental trauma was classified into three basic conditions which are; dental decay, broken teeth and teeth with sharp margins. Patients' ownership of dentures were classified as: none, partial or complete. In addition, patients' oral hygiene habits were classified as: poor or satisfying depending on presence or absence of dental plaque.

We also took patients' tobacco smoking habits into consideration. Related data include years of cigarette usage and the number of cigarettes per day. Similarly, we questioned our patients regarding their history of alcohol consumption. Data taken into consideration include the duration of alcohol drinking and questions about the number of standard glasses drunk per day, week or month for each type of alcoholic beverage. Additionally, former smokers and former drinkers were defined as individuals who had stopped for at least 2 years at the time of the interview. The date of the interview was used as the date of reference for both cases and controls, as cases were interviewed on average within 3 months of diagnosis.

The following variables were used in the analysis: smoking status (never, current, former), quantity (number of cigarettes /day), duration, age at starting and time since quitting tobacco smoking (years). The average daily alcohol consumption was calculated as the number of glasses by adding the average lifetime daily consumption of each type of alcoholic beverage.

Other characteristics of alcohol consumption analyzed were drinking status (never, current, former), duration, age at starting, time since quitting drinking and the average number of glasses/day for every type of alcoholic

beverage. According to UK Department of Health, alcohol consumption for men who drink less than 21 units/week and for women who drink less than 14 units/week is not classified as abusive. In this research, patients who drink less than the above specified quantities were classified as non-drinkers.

Tumor characteristics including grade, stage, location and cervical lymph nodes status in addition to sex, age, smoking and drinking history of patients were extracted from their medical records and analyzed using SPSS software package (revision 13.0 SPSS Inc., Chicago, IL, USA). The variables were analyzed using Chi-square and linear regression analytical tests. The $p < 0.05$ was considered statistically significant.

Results

Patient and control groups were each consist of 30 male and 17 female subjects with mean ages 53,17(± 12.565) and 52.55(± 11.542) respectively. 38 subjects (80.9%) out of 47 were under 40 years old both in patient and control group. Besides age and sex, number of fixed and removable dental prosthesis were matched in each group. 15 subjects (31.9%) out of 47 had removable dental prosthesis whereas 16 subjects (34%) out of 47 had fixed dental prosthesis in each group. Smoking and alcohol abuse proportions were given in Table 1.

Within the patient group non-smokers were 16/47 (34%), 5/47 (10.6%) smoked less then 10 years, 3/47 (6.4%) 10 to 20 years and 23/47 (48.9%) for more then 20 years. 70.2% (33/47) of control group subjects did not smoked and 23.4% (11/47) smoked more then 20 years.

We have determined that 47 Patients, with tongue cancer have mechanical trauma in a rate of 44.7%. On the other hand, 8% has been determined in the control group as well. 47 Patients, with tongue cancer have family history of cancer in a rate of 29.8% but 8.5% has been determined in the control group as well ($\chi^2=8,428$; $p=0.004$).

On regression analysis, alcohol abuse, family history of cancer, smoking, chronic mechanical traumas appeared as significant etiologic factors ($p=0.0001$).

The patients, with tongue cancer and without mechanical trauma in a rate of 34.6% have been diagnosed after examining by at least three and more doctors. On

Table 1. Smoking and Alcohol Abuse in Patient and Control Group

	Smoking		Alcohol	
	(+) No. %	(-) No. %	(+) No. %	(-) No. %
Tongue Ca	31 (66)	16 (34)	13 (27.7)	34 (72.3)
Control group	4 (29.8)	33 (70.2)	-	47 (100)

*For smoking $\chi^2=12,320$; $p < 0.0001$ For alcohol $\chi^2=15,086$; $p < 0.0001$

Table 2. Impact of Mechanical Trauma on Delay Time of Diagnosis (months)

	0	0-2	2-4	4-6	6-8	8-10	>10
	No. (S%)						
Mechanical trauma							
(-)	3 (11.5)	7 (26.9)	3 (11.5)	6 (23.1)	2 (7.7)	2 (7.7)	3 (11.5)
(+)	1 (4.8)	3 (14.3)	6 (28.6)	4 (19)	2 (9.5)	-	5 (23.8)

Table 3. Distribution of Our Patient Group According to TNM Classification

		Female		Male		All patient group	
		No.	%	No.	%	No.	%
Tis		1	(5.9)	-		1	(2.1)
T	1	3	(17.6)	8	(26.7)	11	(23.4)
	2	8	(47.1)	14	(46.7)	22	(46.8)
	3	4	(23.5)	2	(6.7)	6	(12.8)
	4	1	(5.9)	6	(20)	7	(14.9)
N	0	7	(41.2)	13	(43.3)	20	(42.6)
	1	5	(29.4)	8	(26.7)	20	(27.7)
	2	5	(29.4)	8	(26.7)	13	(27.7)
	3	-		1	(3.3)	1	(2.1)
Stage	0	1	(5.9)	-		1	(2.1)
	I	1	(5.9)	7	(23.3)	8	(17)
	II	4	(23.5)	4	(13.3)	8	(17)
	III	6	(35.3)	7	(23.3)	13	(27.7)
	IV	5	(29.4)	12	(40)	17	(36.2)
Diff.	Poor	3	(18.7)	3	(10)	6	(13)
	Moderate	7	(43.8)	16	(53.3)	23	(50)
	Well	6	(37.5)	11	(36.7)	17	(37)

**Figure 1. The 69 Year-old Male Patient has Mechanical Trauma of Removable Dental Prosthesis (T3N0M0)****Figure 2. The 37 Year-old Female Patient has Delaying Diagnosed Tumor of Tongue (T4N2M0). Survived 3 months after diagnosis**

the other hand, the patients, with tongue cancer and mechanical trauma in a rate of 47.6% have been diagnosed after examining by at least three and more doctors ($\chi^2=6,871$; $p=0.009$).

The role of mechanical trauma in tongue carcinomas is may not only be etiologic and delay in diagnosis may be explained as concealing from doctors and patient view in the name of mechanical trauma. The delay of diagnosis and the impact of mechanical trauma were stated in Table 2. And distribution of our patient group according to TNM classification were given in Table 3.

Discussion

Oral cancer is the sixth most common malignancy worldwide with 90% of oral malignancies being squamous cell carcinomas (SCC) (Siegel et al., 2012). Among the different sites within the oral cavity, carcinoma of the tongue is the most seen (Huang et al., 2006; Rao et al., 2013).

The epidemiological evidence confirms that exposure to cigarette use, a complex mixture of more than 4000 particulate and volatile components, increases the incidence of oral carcinogenesis especially in particular

areas, which collect resoluble carcinogens such as floor of mouth and lateral border of tongue of oral cavity. This is a leading cause of cancer deaths throughout the world (Vineis et al., 2004; Rao et al., 2013). Furthermore, exposure to tobacco smoke in non-smokers or different types of usage such as chewing are predispose factors in carcinogenesis. Another known and preventable etiological factors include alcohol abuse, HPV, diets low in fruit and vegetables, dental trauma and poor oral hygiene (Allam et al., 2011; Rao et al., 2013). Interestingly, in India tongue cancer is on the increase in non-smoking non-drinking males (Krishnamurthy and Ramshankar, 2013).

SCC of the tongue, being a disease of the elderly, is very uncommon among young patients. The incidence peaks around sixth to seventh decade of life and is uncommon among people below the age of 40 years (Stolk-Liefferink et al., 2008). In this study, we found 80.9% were under 40 years old both in male and female patients. In Turkey, the starting age for smoking has been declining. Previous studies have highlighted increased risks from current smoking and smoking for 20 years and longer in young patients and even higher risks than in older patients (Llewellyn et al., 2004).

Schantz et al. (1988) hypothesizes that the development of this cancer in young people may be related to a genetic predisposition to environmental carcinogenesis, reflected by chromosomal abnormalities, increased susceptibility to mutagen-induced chromosome damage, or DNA repair deficiency (Schantz et al., 1988). Further research is needed to explain whether other, perhaps genetic (familial) or viral, risk factors are indeed present to account for the development of tongue cancer in young patients.

Squamous cell carcinoma of the tongue especially occurs in men (Neville et al., 2002; Schmidt et al., 2004; Sturgis et al., 2004; Vineis et al., 2004; Massano et al., 2006). In study group, the male:female ratio is 63.8:36.2, respectively. The difference can be attributed to the possible differences in habitual actions such as smoking and drinking between males and females. Other reports, however, have shown no sex difference (Clark et al., 1992). On the other hand, carcinoma of the tongue has widely been regarded as a disease predominantly affecting males. Jones et al. reported female patients with carcinoma of the tongue outnumbering males by almost 2:1 in patients under 40 years old and similar findings have been reported by Callery et al. (1984) and Jones et al. (1989). This change in the incidence can be due to increased trends of smoking and/or drinking in women and the greater prevalence in men can be caused by their more exposure to occupational carcinogens, toxins and the other risk factors like marijuana compared to women.

Tobacco and alcohol have long been implicated in the etiology of tongue cancer in older adults (Schmidt et al., 2004; Sturgis et al., 2004; Vineis et al., 2004; Warnakulasuriya et al., 2009; Albuquerque et al., 2011). However, little is known about what the contribution of these same risk factors are in younger patients diagnosed with tongue cancer (Clark et al., 1992). We found that 66% of the study group had smoked and half of them have been smoking longer than 20 years despite of this approximately 70% of control group have never smoked.

Alcohol abuse proportion was 27.7% in our patient group whereas no one in control group had drunk alcohol. These results concur with the literature.

Chronic trauma of tongue and its causative role on oral carcinogenesis is a dilemma. Some authors suggested it as a cause of oral cancer; on the other hand, others suggest it is a result of the increase in volume of the tumor (Piemonte et al., 2010). In our study, results show significant association between chronic trauma and tongue cancer: 44.7% of the patients with tongue cancer had chronic trauma, whereas control groups exhibited a far lower percentage as 17% of trauma. Our results are consistent with the hypothesis that chronic physical irritation of the tongue squamous epithelium by a broken tooth or an inappropriately fitted denture may promote dysplasia and carcinogenesis, and this is independently of other risk factors (Behnoud et al., 2011). Lockhart et al. (1998) did not find statistically significant results for association between oral cancer and dental factors, including tooth loss, defective teeth and denture use (Lockhart et al., 1998). Studies by Talamini and Rosenquist link dental status with oral cancer risk using control group randomly conformed (Talamini et al., 2000; Hansson et al., 2005).

It is hypothesized that field cancerization is evident in oral and orofarengeal mucosa (in the existence of epigenetic factors) with multiple steps of molecular changes starting from the first sign of dysplasia or other preneoplastic condition (Al Attas et al., 2014). In our opinion, the nuance is that, the site of chronic trauma reaches the point of cancer before any other competitive sites of oral mucosa. And moreover the very early signs of cancer can conceal from suspicious eyes under the name of chronic trauma. Molecular based further investigations are needed to understand the impact of chronic trauma on oral carcinogenesis. Finally, the role of otolaryngologists and dentists for oral screening and detecting oral cancers are valuable and should not be forgotten.

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