Review Article

Clinicopathological differences between lip cancers and tongue cancers

Alberto Rodriguez-Archilla, Alicia Almagro-Garcia

Department of Stomatology, Oral Medicine Unit, Faculty of Dentistry, University of Granada, Granada, Spain

Abstract

Lip cancer is closely linked to chronic exposure to solar radiation, while tongue cancer, the most common intraoral neoplasm, is mainly related to tobacco and/or alcohol consumption. Lip cancer has a much better prognosis than tongue cancer. The objective of this study was to assess the differentiating features between squamous cell carcinomas located on both the lip and the tongue. A search for studies on lip cancer and tongue cancer was performed in the following databases: PubMed (MEDLINE and Cochrane Library), Web of Science (WoS), and Scopus. The estimated prevalence of lip and tongue cancers was calculated according to the random model of DerSimonian and Laird. For categorical outcomes, Pearson's Chi-square test was used with Fisher's exact test when required. Thirty-two studies were included in this review. Considering the whole oral tumor locations, the estimated prevalence of lip cancer was 23.43% and in tongue cancer, 27.58%. A greater number of lip cancers were found in males, were classified as T1, were well-differentiated tumors, and had a higher 5-year survival rate. In contrast, a greater number of tongue cancers were observed in younger patients, tobacco and/or alcohol users, presented lymph node metastases, and more advanced tumor stages. Although both tumors are located in the mouth, lip cancers and tongue cancers have different clinicopathological features and biological behaviors.

Keywords: Lip neoplasms, oral manifestations, prognosis, tongue neoplasms

Address for correspondence: Prof. Alberto Rodriguez-Archilla, Department of Stomatology, Oral Medicine Unit, Faculty of Dentistry, Colegio Maximo, s/n. Campus De Cartuja, Granada 18071, Spain.
E-mail: alberodr@ugr.es

INTRODUCTION

Head-and-neck cancers are the sixth most frequent type of malignant tumor in the world, with a relevant prevalence in South-Central Asia where they are the third most frequent type of cancer. Mouth neoplasms can be differentiated into three areas: (1) lip cancer, (2) intraoral cancer that includes the inner labial mucosa, the tongue and floor of the mouth, the buccal mucosa, the gums, and the hard palate; and (3) oropharyngeal cancer that contains the base of the tongue, the soft palate, and tonsils. Tumors located in each of these three locations have different clinical-pathological and prognostic characteristics.[1]

Lip cancer is a frequent and highly curable tumor, especially when it is detected early, with 5-year survival rates above 85%. However, up to 20% of cases present lymph node metastases and 15% may have an aggressive behavior with recurrences and a higher mortality rate. More than 90% of cases affect the lower lip. Although lip cancer has been

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more frequently classified as oral cancer, the authors choose to consider lip cancer as one of the facial skin cancers. Its biological behavior is more similar to squamous cell carcinoma of the skin of the face than to that of carcinoma of the oral mucosa. There are also differences regarding its etiological agents. In lip cancer, the main agent is ultraviolet radiation, while in tongue cancer, they are the consumption of tobacco and/or alcohol.[2]

Tongue cancer is the most common intraoral malignant tumor, affecting, above all, the lateral edges and tongue ventral side. Its diagnosis is usually delayed, and this conditions a lower 5-year survival rate that is around 52%. The main carcinogenic agent related to this tumor is tobacco use. Alcohol, by itself, is also a risk factor, although it is a less potent carcinogen than tobacco. In people who use tobacco and alcohol, these risk factors appear to be synergistic and result in a multiplicative increase in risk, 30–36 times higher for people who smoke and drink in large amounts.[3] However, in recent years, an increase in the incidence of tongue cancers has been observed in the younger population without relevant harmful habits of tobacco and alcohol consumption, whose appearance is related to human papillomavirus (HPV) infection in 2%–20% of cases. However, HPV infection is exceptionally observed in lip cancers.[4]

This study aimed to analyze the differentiating features between squamous cell carcinomas localized on both the lip and the tongue.

METHODS

Search strategy and study selection criteria

A search for studies up to June 2021 on lip and tongue cancers was conducted in the following databases: PubMed (MEDLINE and Cochrane Library), Web of Science (WoS), and Scopus. Search strategies were developed for each database with a combination of Medical Subject Headings (MeSH) and free-text terms. Searched terms were the following: "tongue neoplasms" [MeSH Terms] AND "lip neoplasms" [MeSH Terms]; ("tongue cancer" AND "lip cancer") OR ("tongue neoplasms" AND "lip neoplasms"); and TITLE-ABS-KEY (("tongue cancer" AND "lip cancer") OR ("tongue neoplasms" AND "lip neoplasms")). The exclusion criteria were as follows: (a) articles without full-text availability, (b) studies that did not consider lip cancer and tongue cancer jointly, (c) studies on tumors that are not squamous cell carcinomas, and (d) studies with nonusable data.

Statistical analysis

The data were analyzed with the program MedCalc Statistical Software version 20.019 (MedCalc Software Ltd., Ostend, Belgium) to calculate the estimated prevalence according to the random model of DerSimonian and Laird. The program IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA) was also used for a descriptive statistic (number of cases, percentages), and for the comparison of categorical variables, Pearson's Chi-square test was used with Fisher's exact test when required. A value of $P < 0.05$ was considered statistically significant.

RESULTS

In the initial search, 1497 articles were found (436 in PubMed, 542 in WoS, and 519 in Scopus), 540 of them duplicates, leaving 957 articles to eligibility. The exclusion criteria were as follows: (a) articles without full-text availability (n = 189), (b) studies that did not jointly consider cases of lip cancer and tongue cancer (n = 360), (c) studies on non-squamous cell carcinomas (n = 142), and (d) studies with nonusable data (n = 234). After applying these criteria, 32 studies were included in this revision [Figure 1].

Table 1 presents the prevalence of lip cancer in 128,536 cancer patients considered in 23 studies.[5-27] The estimated global prevalence of lip cancer was 23.43% (95% confidence interval [CI]: 16.22%–31.59%). In the different studies, the prevalence ranged from the maximum prevalence of 63.97% (95% CI: 62.02%–65.88%)[8] to the minimum of 1.24% (95% CI: 0.15%–4.41%).[11]

The prevalence of tongue cancer in 128,536 cancer patients included in 23 studies[5-27] is shown in Table 2. The estimated global prevalence of tongue cancer was 27.58% (95% CI: 23.88%–31.44%). In the different studies, the prevalence ranged between a maximum prevalence of 65.78% (95% CI: 61.79%–67.68%)[14] and a minimum of 9.27% (95% CI: 7.15%–11.77%).[22]

Table 3 exhibits the comparison of different clinicopathological parameters between lip cancers and tongue cancers. In patients over 55, cancers of the lip were slightly more common than those of the tongue, while in the younger population (<55 years), tongue tumors were more frequent than those of the lip. After the statistical analysis, a significant relationship was found (P = 0.01). According to gender, a high percentage of men (almost 80%) and a lower percentage of women (66.4%) with lip cancers were observed, with a highly significant statistical association ($P < 0.001$). Considering harmful habits (tobacco

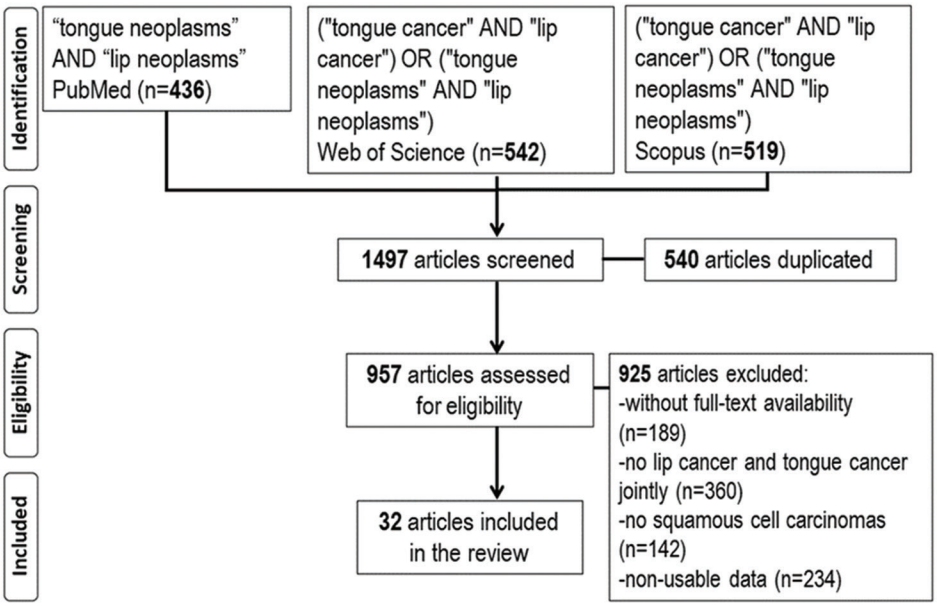

Figure 1: Study flow diagram

Table 1: Estimated prevalence (and 95% confidence interval) of lip cancer in the different studies

Study, year	Country	*n*	Prevalence (%)	95% CI
Fries *et al*., 1980[5]	Germany	585	19.31	16.19-22.75
Fahmy *et al*., 1983[6]	Iran	370	50.27	45.05-55.48
Silverman and Gorsky, 1990[7]	USA	20,115	21.85	21.28-22.42
Pukkala *et al*., 1994[8]	Finland	2423	63.97	62.02-65.88
Ostman *et al*., 1995[9]	Sweden	11,832	44.53	43.63-45.43
Izarzugaza *et al*., 2001[10]	Spain	2435	24.27	22.57-26.02
Kerdpon and Sriplung, 2001[11]	Thailand	161	1.24	0.15-4.41
Tarvainen *et al*., 2004[12]	Finland	11,992	61.45	60.57-62.32
Hogan *et al*., 2005[13]	Australia	101	12.87	7.03-21.00
Sargeran *et al*., 2006[14]	Iran	1042	14.01	11.96-16.26
Oji and Chukwuneke, 2007[15]	Nigeria	81	14.81	7.89-24.44
Popović *et al*., 2007[16]	Serbia	26	30.77	14.32-51.79
Al-Rawi and Talabani, 2008[17]	Iraq	1425	22.17	20.04-24.42
Andisheh-Tadbir *et al*., 2008[18]	Iran	200	6.00	3.13-10.24
Effiom *et al*., 2008[19]	Nigeria	233	7.72	4.64-11.93
Murthy *et al*., 2010[20]	India	1180	2.37	1.58-3.41
Vatanasapt *et al*., 2011[21]	Thailand	1038	27.45	24.76-30.28
Zini *et al*., 2012[22]	Israel	647	27.35	23.95-30.96
Listl *et al*., 2013[23]	Germany	15,792	7.49	7.08-7.91
Farah *et al*., 2014[24]	Australia	55,421	43.88	43.46-44.29
Khammissa *et al*., 2014[25]	India	554	6.49	4.59-8.88
Ali *et al*., 2016[26]	Pakistan	77	51.95	40.25-63.48
Alves *et al*., 2017[27]	Brazil	806	30.89	27.71-34.21
Total (random effects)*		128,536	23.43	16.22-31.59
Test for heterogeneity: Q=18793.63, df: 22 (P<0.0001), I^2=99.88%, 95% CI: 99.87-99.89				

*DerSimonian and Laird random effects model. *n*: Sample size, CI: Confidence interval, USA: United States of America

and/or alcohol consumption), there were higher percentages of smokers (72.3%) and/or drinkers (64.4%) with tongue cancer compared to lip cancer, with statistically significant differences ($P < 0.01$ in both cases).

Regarding tumor size (T parameter), the majority of tongue tumors were larger (T2, T3, and T4) compared to most lip tumors that were smaller (T1), with a highly significant statistical relationship ($P < 0.001$). Similarly, tongue cancers presented lymph node metastases (parameter N) more frequently than those of the lip, finding a highly significant statistical association ($P < 0.001$). Considering the tumor differentiation degree, most lip cancers were well-differentiated tumors, while a significant percentage of tongue cancers were moderately or poorly differentiated tumors. Statistical analysis showed significant differences ($P = 0.01$).

Table 2: Estimated prevalence (and 95% confidence interval) of tongue cancer in the different studies

Study, year	Country	*n*	Prevalence (%)	95% CI
Fries *et al*., 1980[5]	Germany	585	14.53	11.77-17.65
Fahmy *et al*., 1983[6]	Iran	370	20.27	16.29-24.73
Silverman and Gorsky, 1990[7]	USA	20,115	25.04	24.44-25.64
Pukkala *et al*., 1994[8]	Finland	2423	18.28	16.76-19.88
Ostman *et al*., 1995[9]	Sweden	11,832	21.71	20.97-22.46
Izarzugaza *et al*., 2001[10]	Spain	2435	27.92	26.15-29.75
Kerdpon and Sriplung, 2001[11]	Thailand	161	47.20	39.29-55.21
Tarvainen *et al*., 2004[12]	Finland	11,992	19.21	18.51-19.93
Hogan *et al*., 2005[13]	Australia	101	35.64	26.36-45.79
Sargeran *et al*., 2006[14]	Iran	1042	64.78	61.79-67.68
Oji and Chukwuneke, 2007[15]	Nigeria	81	27.16	17.86-38.18
Popović *et al*., 2007[16]	Serbia	26	34.61	17.21-55.66
Al-Rawi and Talabani, 2008[17]	Iraq	1425	11.86	10.22-13.65
Andisheh-Tadbir *et al*., 2008[18]	Iran	200	53.00	45.83-60.07
Effiom *et al*., 2008[19]	Nigeria	233	17.59	12.93-23.10
Murthy *et al*., 2010[20]	India	1180	26.95	24.43-29.57
Vatanasapt *et al*., 2011[21]	Thailand	1038	18.78	16.45-21.29
Zini *et al*., 2012[22]	Israel	647	9.27	7.15-11.77
Listl *et al*., 2013[23]	Germany	15,792	39.52	38.75-40.28
Farah *et al*., 2014[24]	Australia	55,421	19.79	19.45-20.12
Khammissa *et al*., 2014[25]	India	554	37.00	32.97-41.17
Ali *et al*., 2016[26]	Pakistan	77	48.05	36.51-59.74
Alves *et al*., 2017[27]	Brazil	806	27.04	24.01-30.25
Total (random effects)*		128,536	27.58	23.88-31.44
Test for heterogeneity: Q=3865.51, df: 22 (P<0.0001), I^2=99.43%, 95% CI: 99.36-99.50				

*DerSimonian and Laird random effects model. *n*: Sample size, CI: Confidence interval, USA: United States of America

Table 3: Analysis of the different parameters in both lip and tongue cancers

Parameter	Reference number	Lip cancer, *n* (%)	Tongue cancer, *n* (%)	*P*
Age group (years)				
<55	[14-16,22,23,26,28-31]	514 (30.2)	2233 (33.9)	0.01*
>55		1188 (69.8)	4456 (66.1)	
Gender				
Males	[5-10,12,14-19,22-24, 26,31-35]	33278 (79.2)	16621 (66.4)	<0.001*
Females		8709 (20.8)	8407 (33.6)	
Tobacco				
Yes	[16,28-31,34]	57 (54.3)	146 (72.3)	<0.01*
No		48 (45.7)	56 (27.7)	
Alcohol				
Yes	[16,28-31,34]	43 (43.9)	121 (64.4)	<0.01*
No		55 (56.1)	67 (35.6)	
Tumor size				
T1	[5,27,31,32]	262 (77.5)	107 (37.0)	<0.001*
T2–T3–T4		76 (22.5)	182 (63.0)	
Lymph node metastases				
N(−)	[5,27,32,36]	150 (69.1)	98 (46.2)	<0.001*
N(+)		67 (30.9)	114 (53.8)	
Tumor differentiation degree				
WD	[18,19,26,34]	61 (72.6)	131 (56.5)	0.01*
MD-PD		23 (27.4)	101 (43.5)	
Tumor stage				
I	[7,11,32,34]	1512 (81.4)	1171 (30.6)	<0.001*
II–III–IV		345 (18.6)	2661 (69.4)	
Survival time (months)				
<60	[7,28-31]	170 (8.2)	1489 (57.8)	<0.001*
>60		1889 (91.8)	1086 (42.2)	

*Statistically significant. *n*: Number of cases, T1: Tumors up to 2 cm in diameter, T2–T3–T4: Tumors >2 cm and/or affecting adjacent tissues, N(−): No lymph node metastases, N(+): With lymph node metastases, WD: Well-differentiated, MD-PD: Moderately-poorly differentiated

The tumor stage was also analyzed, observing more than 80% of stage I lip tumors, while among tongue tumors, this percentage decreased to 30.6%, with a highly significant statistical relationship ($P < 0.001$).

Finally, the 5-year survival rate was much higher in lip cancer patients compared to tongue cancer patients, showing a highly significant statistical association ($P < 0.001$).

DISCUSSION

In the present revision on the differentiating clinicopathological features between lip cancers and tongue cancers, 32 studies were included.

In this study, an estimated prevalence of 23.43% for lip cancer and 27.58% for tongue cancer was found in a population of 128,536 patients with mouth cancer considered in 23 studies.[5-27] In the case of lip neoplasms, this high prevalence is justified by the prolonged and continuous exposure to solar radiation related to the type of outdoor occupation and the greater susceptibility of people with low skin phototypes (light skin color). Most tongue tumors affect the lateral border/ventral tongue surface, areas that favor the spread of the tumor and the development of lymph node metastases, worsening the clinical course and the prognosis of these lesions.[27] The main etiological factors of tongue cancer, unlike lip cancer whose main etiological factor is chronic sun exposure, are tobacco and/or alcohol consumption and, above all, its combined consumption.[25]

On the other hand, among patients older than 55 years, 69.8% had lip cancer compared to 66.1% with tongue cancer, with statistically significant differences ($P = 0.01$). All studies show that as you get older, the chance of developing oral cancer increases. Older age supposes a weakening of the antitumor immune system together with a greater action of the different carcinogenic agents (tobacco consumption, alcohol intake, poor lifestyles, etc.) for a longer time throughout life.[14] In lip cancer, due to its slow evolution, age is not as relevant a prognostic factor as in the case of tongue cancer.[15]

Furthermore, neoplasms have a marked predilection for the male gender (79.2% of males for lip cancer and 66.4% of males for tongue cancer), with a highly significant statistical association ($P < 0.001$). This higher prevalence in men can be attributed to harmful habits (tobacco and/or alcohol consumption) that are much more frequent in males than in females.[26] Moreover, in the case of lip cancer, women tend to be more sensitive to the use of protective measures against solar radiation.[24]

Tobacco was a more influential factor in tongue cancer (72.3% of smokers) than in lip cancer (54.3% of smokers), with a statistically significant relationship ($P < 0.01$). Smoking is the main risk factor for oral cancer. Tobacco smoke reduces antioxidant levels in the oral mucosa, increasing free radicals and oxidative stress, damaging mitochondrial DNA, and inducing mutations in oral epithelial cells.[30] Tobacco probably has a greater effect on tongue cancer because its action takes place inside the oral cavity with a greater persistence of carcinogenic substances, unlike the lip, which is an external environment where their action is punctual, especially the lip area where the cigarette is placed that has greater contact with the filter paper.[31]

Regarding alcohol, there was a higher percentage of drinkers in patients with tongue cancer (64.4%) compared to patients with lip cancer (43.9%), and there were also statistically significant differences ($P < 0.01$). Acetaldehyde, a carcinogen generated by alcohol metabolism, is another oral carcinogenic agent independent of tobacco, although its action is increased when it acts synergistically with it. Acetaldehyde interferes with DNA synthesis and repair and induces the atrophy of oral epithelial cells. It develops a direct toxic or oxidative effect on the epithelium and increases the permeability of the oral mucosa to other carcinogens such as tobacco.[30] The fact that there is a longer contact time of alcohol with the oral mucosa than with the lip could explain this greater implication of alcohol in tongue cancer.[29]

Three-quarters (77.5%) of lip tumors were lesions up to 2 cm in diameter (T1) compared to almost two-thirds (63%) of tongue tumors that were larger lesions (T2–T3–T4). In the statistical analysis, a highly significant association was found ($P < 0.001$). Several reasons could explain this smaller size of lip cancers: (1) the location allows a direct inspection of the area and an earlier diagnosis of the lesion; (2) the appearance of labial lesions in the form of an ulcer with a bleeding tendency is the main reason for the patient's consultation, and (3) the lesions in these initial stages are localized and have a better treatment with less morbidity and a high survival rate.[27] Conversely, cancers located on the lateral-posterior tongue or the ventral tongue side, usually are little symptomatic until they are advanced lesions. For these reasons, their diagnosis is delayed.[32]

Lymph node metastases (N+) are another differentiating parameter of lip and tongue cancers. Less than a third (30.9%) of the lip cancers and more than half (53.8%) of the tongue cancers had lymph node metastases, also observing a highly significant statistical relationship ($P < 0.001$). Due to its earlier diagnosis, its location in the lip, and its slow evolution of biological behavior, lip cancers are lesions with a lower tendency to lymph node metastases. In contrast, tongue tumors are located in a highly vascularized anatomical area that favors dissemination; their biological behavior is more aggressive, with larger and more evolved lesions at the time of diagnosis.[32]

In this study, 72.6% of the lip cancers were well-differentiated tumors, while 43.5% of the tongue cancers were moderately-poorly differentiated lesions with statistically significant differences ($P = 0.01$). Lip tumors have a much less aggressive biological behavior than lingual tumors, generally being lesions with a good tumor differentiation degree. Tongue tumors have a worse biological behavior with proliferative activity and a greater probability of dysplastic changes that confer worse tumor differentiation.[26]

In the present work, 81.4% of lip tumors and 30.6% of tongue cancers were classified as tumor stage 1, with a highly significant statistical association ($P < 0.001$). The smallest size, the lower tendency to metastasis, and a slow, progressive growth biological behavior were the parameters that could justify this very high percentage of stage 1 lip cancers. These same reasons in the opposite direction would be those that would explain that almost 70% of tongue cancers are classified in the most advanced tumor stages.[32]

Finally, 91.8% of patients with lip cancer had a survival rate >60 months, while in patients with tongue cancer, this percentage fell to 42.2%, finding a highly significant statistical relationship ($P < 0.001$). Tongue cancer, due to the great vascularization of the area, has a great infiltrative tendency to spread to adjacent tissues with a high rate of local invasion and regional and distant metastasizing capacity. On the other hand, lip cancers have a much better prognosis due to their slow growth and long evolution, apart from the greater ease of treatment.[30]

New studies are required with a longer follow-up time of patients with cancers of both the lip and the rest of intraoral locations that examine further the biological behavior of these neoplastic lesions and their clinical and prognostic repercussions.

CONCLUSIONS

In this revision, considering all the mouth tumors, the estimated prevalence of lip cancer was 23.43% and in tongue cancer, 27.58%. A greater number of lip cancers were found in males, were classified as T1, were well-differentiated tumors, and had a higher 5-year survival rate. In contrast, a greater number of tongue cancers were observed in younger patients, tobacco and/or alcohol users, with more frequent lymph node metastases and more advanced tumor stages.

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Conflicts of interest
There are no conflicts of interest.

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