

## The Analysis of Oral Cancer on Pubmed from 2012 to 2016

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### Review Article

Received date: 14/07/2017

Accepted date: 26/08/2017

Published date: 28/08/2017

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**Keywords:** Oral cancer, Region, Gender,  
Histopathology, Treatment

#### ABSTRACT

**Background and objective:** Oral cancer has become a global threat of human health. There were various of epidemiological reports all around the world. With the increase of oral cancer epidemiology in recent years, we aim to study the prevalence of oral cancer by searching literatures in last 5 years to observe if there were changes of anatomical sites, gender, age and histopathology and treatment. **Methods:** We conduct a systemic review on the prevalence of oral cancer around five continents from January 2012 to December 2016. 1. According to the requisition of systematic evaluation, we formulated detailed standardization of the inclusion and exclusion criteria which include the pathological type of cancer and the time of publication. 2. We searched literatures in Pubmed databases from January 2012 to December 2016. The following search terms were used: Mouth neoplasm or Oral neoplasm or mouth cancer or oral cancer and epidemiology.

**Results:** A total of 4,310 literatures were reported worldwide during the period of study by selecting through the Pubmed search engines. After exclusion of duplicate or irrelevant references, 4,283 were excluded. 27 full articles were assessed, which include 231,688 oral cancer patients from 18 countries and regions. 1. In a total of 231,688 patients, there was a higher incidence of cancer in the tongue with 112,643 cases (48.6%), followed by the lip 35,185 (15.2%), buccal mucosa 25,817 cases (11.1%), palate 12,942 cases (5.6%), gingiva 10,239 cases (4.4%), floor of mouth 9,924 cases (4.3%), and 24,938 cases (10.8%) in the mixed sites and NOS (not otherwise specified). 2. In this study, the tongue was the most frequent anatomical site in Asia, Europe, North America and South America, while the lip was the most common site in Oceania. 3. Geographically, North America (44.4%) was where majority of the oral cancer came from. Followed by the Oceania (20.2%), Europe (17.5%), Asia (15.2%) and the least number of patients in South America (2.7%). 4. A total of 77,228 patients have the gender information, among which 54,061 (70%) were men and 23,167 (30%) were women. The male-to-female ratio was 2.3:1. Differences were noticed when divided by subsite: the floor of mouth (3.2:1), the tongue (2.2:1), the buccal mucosa (1.8:1), the palate (1.5:1), the gingiva (1.3:1) and the mixed sites and NOS (1.6:1). A total of 130,534 patients were reported from Asia, Europe, Oceania, North America and South America. Slightly more males than females were affected by oral cancer. The highest male-to-female ratio was Asia at 4.8:1, followed by the Oceania at 2.4:1, the Europe at 1.9:1, the South America at 1.8:1 and the North America at 1.6:1. 5. There were 10,813 patients who have the age information, 9,822 (90.8%) were older than 40 years and 991 (9.2%) were younger than 40. 6. Histopathologic type was as follows: 53,908 cases (95.7%) of squamous cell carcinoma, 2,431 cases (4.3%) of non-squamous cell carcinoma. 7. There was only 1 article concluded 6830 oral cancer patients with treatment details and survival in total of 27 full articles. This study indicated that surgery was effective for 6830 patients diagnosed as stage I or II oral cancer. Full

survival rate of 5 years of 6830 patients treated with surgery was 69.7%. 5-year survival rates of 3298 patients treated with neck dissection (71.7%) were higher than 3448 patients without neck dissection (68.0%),  $P=0.001$ . However, 5-year survival rates of 1231 patients treated with radiation therapy (57.5%) were lower than 5468 patients without radiation therapy (72.7%),  $P<0.001$  and 187 patients with chemotherapy (53.5%) were lower than 6490 patients without chemotherapy (69.0%),  $P<0.001$ .

**Conclusion:** 1. Coordinate with the earlier knowledge, this current review suggested that the tongue was the site with the highest risk for oral cancer from a global perspective also on a regional level in Asia, Europe, North America and South America. However, the lip was the most common site for oral cancer in Oceania. 2. North America has the most oral cancer patients according to the investigation. We are not sure at this time point if it was because a high incident rate of the disease in this region or it may be due to the amount of effort researchers put in. 3. Males are more susceptible to oral cancer. 4. Majority of the patients is with an age over 40. 5. The most common oral cancer is squamous cell carcinoma. 6. Surgery is an effective treatment for early oral cancer.

## **INTRODUCTION**

Oral epithelial cancer was an invasive tumor with dysplasia on oral mucosa, including squamous cell carcinoma, basal cell carcinoma and adenocarcinoma. The cause of oral cancer was unclear, the main risk factors included smoking, drinking, virus and fungus infection, occupation, bad prosthesis and oral diseases [1,2]. Betel nut was a common cause in Southeast Asia [3]. The clinical symptom of oral cancer in early stage was nonspecific. Oral mucosa diseases such as oral leukoplakia (OLK) and oral lichen planus (OLP) can become oral cancer by malignant transformation, showing a red or white lesion. Oral cancer could be associated with ulcers, pain, bad breath, difficulty of speaking, chewing and swallowing and invaded surrounding bone and nerve tissue. The 5-year survival rate of oral cancer patients was 64% with a poor prognosis [4]. The incidence of oral cancer has changed with habits, diets, environment and health. Reports varied from region to region. To provide theoretical basis for further study on prevention and treatment of oral cancer, we searched literatures in the past 5 years to perform an analysis of the trends and clinicopathologic features.

## **MATERIALS AND METHODS**

### **Literature Search**

A comprehensive literature search was performed in PubMed databases from January 2012 to December 2016. The following search terms were used: (mouth neoplasm or oral neoplasm or mouth cancer or oral cancer) and epidemiology. We also performed manual searches of relevant literatures.

### **Objective of The Study**

#### **Standardization of the inclusion**

(1) Literatures published from January 2012 to December 2016. (2) Literatures came from Asia, Europe, Oceania, North America and South America, without Africa. (3) Oral cancer was diagnosed by histopathology. (4) According to the UICC (Union for International Cancer Control), we restricted the analysis to the following sites: lip, tongue, floor of mouth, buccal mucosa, gingiva, palate, mixed sites and NOS.

#### **Standardization of the exclusion**

(1) Studies were performed on animal, cell and gene. (2) Oral cancer was unclassified.

## **RESULTS**

### **Characteristics of Eligible Studies**

Based on our search strategy, a total of 4,310 literatures were searched. 27 eligible literatures [5-31] were identified by reading title, abstract and full text. Of the 27 studies, 231,688 oral cancer patients were included from 18 countries and regions: Yemen, India, Israel, Japan, Singapore, Iran, Korea and Taiwan in Asia; Britain, Germany, Portugal, Norway and Netherlands in Europe; The USA, Mexico and Canada of in North America; Brazil in South America and Australia in Oceania.

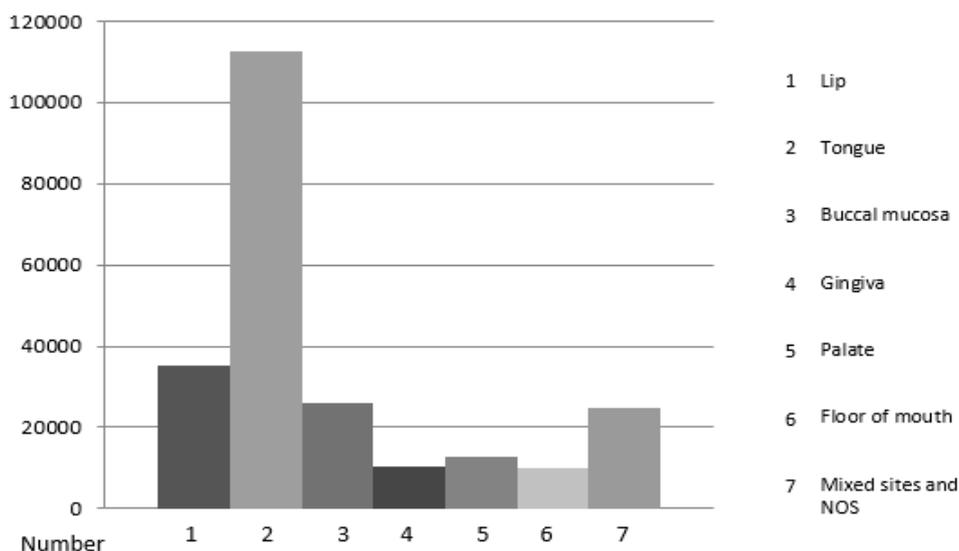
**Analysis Results**

**Anatomical sites of oral cancer**

In a total of 231,688 patients, there is a higher incidence of cancer in the tongue with 112,643 cases (48.6%), followed by the lip 35,185 (15.2%), buccal mucosa 25,817 cases (11.1%), palate 12,942 cases (5.6%), gingiva 10,239 cases (4.4%), floor of mouth 9,924 cases (4.3%), and 24,938 cases (10.8%) in the mixed sites and NOS (**Table 1**) (**Figure 1**).

**Table 1.** Anatomical sites of oral cancer.

Site of the tumors	Number	Percentage (%)
Lip	35185	15.2
Tongue	112643	48.6
Buccal mucosa	25817	11.1
Gingiva	10239	4.4
Palate	12942	5.6
Floor of mouth	9924	4.3
Mixed sites and NOS	24938	10.8
Total	231688	100.0



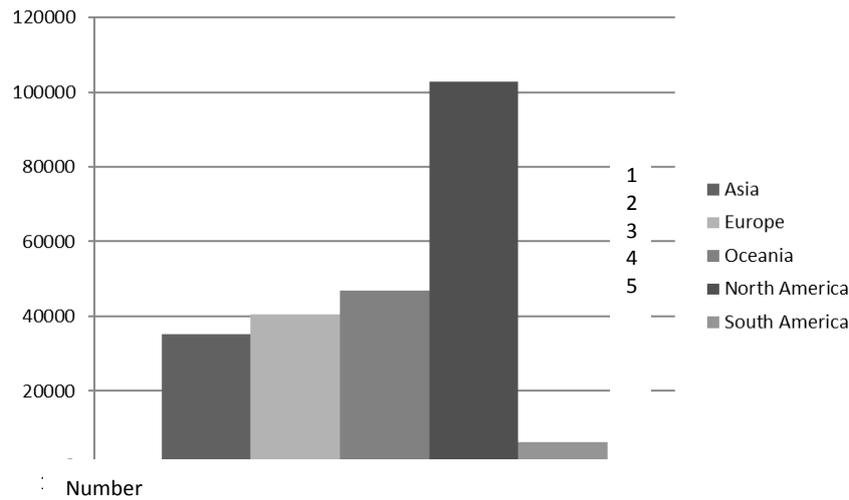
**Figure 1.** Anatomical sites of oral cancer.

**Geographic distribution of oral cancer**

Geographically, North America (44.4%) is where majority of the oral cancer came from. Followed by the Oceania (20.2%), Europe (17.5%), Asia (15.2%) and the least number of patients in South America (2.7%). There were two possibilities, first was the scholars in South America ignored, second was the low incidence in South America and deficiency of cases (**Table 2**) (**Figure 2**).

**Table 2.** Geographic distribution of oral cancer.

Regions	Number	Percentage (%)
Asia	35321	15.2
Europe	40485	17.5
Oceania	46799	20.2
North America	102885	44.4
South America	6198	2.7
Total	231688	100.0



**Figure 2.** Geographic distribution of oral cancer.

**Anatomical sites of oral cancer distribution in different geographic regions**

In this study, the tongue was the most frequent anatomical site in Asia, Europe, North America and South America, while the lip was the most common site in Oceania (**Table 3**).

**Table 3.** Anatomical sites of oral cancer distribution in different geographic regions.

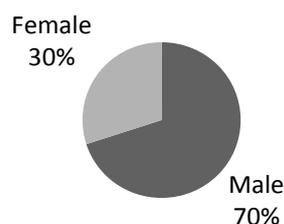
Sites	Asia	Europe	Oceania	North America	South America
Lip	287 (0.8)	1707 (4.2)	24320 (52.0)	8807 (8.6)	64 (1.0)
Tongue	14615 (41.4)	15704 (38.8)	10968 (23.4)	69148 (67.2)	2208 (35.6)
Buccal mucosa	9584 (27.1)	32 (0.1)	0 (0.0)	600 (0.6)	23 (0.4)
Gingiva	1214 (3.4)	2494 (6.2)	1539 (3.3)	7428 (7.2)	267 (4.3)
Palate	1513 (4.3)	2435 (6.0)	2593 (5.5)	2247 (2.2)	1136 (18.3)
Floor of mouth	1167 (3.3)	9818 (24.3)	4330 (9.3)	9269 (9.0)	1233 (19.9)
Mixed sites and NOS	6941 (19.7)	8295 (29.5)	3049 (6.5)	5386 (5.2)	1267 (20.4)
Total	35321 (100.0)	40485 (100.0)	46799 (100.0)	102885 (100.0)	6198 (100.0)

**Gender distribution of oral cancer**

A total of 77,228 patients, 54,061 (70%) were men and 23,167 (30%) were women. The male-to-female ratio was 2.3:1, with more male cases (**Table 4**) (**Figure 3**).

**Table 4.** Gender of oral cancer distribution.

Sex	Number	Percentage
Male	54061	70.0%
Female	23167	30.0%
Total	77228	100.0%



**Figure 3.** Percentage of gender.

**Anatomical sites and gender distribution of oral cancer**

There were differences by subsite: the male-to-female ratio of the floor of mouth was the highest at 3.2:1 (7,806/2,465),

followed by 2.2:1 (16,585/7,594) in the tongue, 1.8:1 (885/480) in the buccal mucosa, 1.5:1 (2,034/1,328) in the palate, 1.3:1 (1,546/1,203) in the gingiva and 1.6:1 (5,823/3,629) in the mixed sites and NOS (**Table 5**).

**Table 5.** Anatomical sites and gender distribution of oral cancer.

Sites	Male (%)	Female (%)	Total
Up	19382 (75.0)	6468 (25.0)	25850
Tongue	16585 (68.6)	7594 (31.4)	24179
Buccal mucosa	885 (64.8)	480 (35.2)	1365
Gingiva	1546 (56.2)	1203 (43.8)	2749
Palate	2034 (60.5)	1328 (39.5)	3362
Floor of mouth	7806 (76.0)	2465 (24.0)	10271
Mixed sites and NOS	5823 (61.6)	3629 (38.4)	9452

**Geographic and gender distribution of oral cancer**

A total of 130,534 patients were reported from Asia, Europe, Oceania, North America and South America. Slightly more males than females were affected by oral cancer. The highest male-to-female ratio was Asia at 4.8:1 (27,494/5,723), followed by the Oceania at 2.4:1 (32,967/13,832), the Europe at 1.9:1 (20,855/10,770), the South America at 1.8:1 (573/316) and the North America at 1.6:1 (11,131/6,873) (**Table 6**).

**Table 6.** Geographic and gender distribution of oral cancer.

Regions	Male (%)	Female (%)	Total
Asia	27494 (82.8)	5723 (20.8)	33217
Europe	20855 (65.9)	10770 (34.1)	31625
Oceania	32967 (70.4)	13832 (29.6)	46799
North America	11131 (61.8)	6873 (38.1)	18004
South America	573 (64.5)	316 (35.5)	889

**Age distribution of oral cancer**

There were 10,813 patients who have the age information, 9,822 (90.8%) were older than 40 years and 991 (9.2%) were younger than 40 (**Table 7**).

**Table 7.** Age of oral cancer distribution.

Age	Number	Percentage (%)
<40	991	9.2
≥ 40	9822	90.8
Total	10813	100.0

**Histopathologic type**

Histopathologic type was as follows: 53,908 cases (95.7%) of squamous cell carcinoma, 2,431 cases (4.3%) of non-squamous cell carcinoma, as same as the reports of textbook and other literatures (**Table 8**).

**Table 8.** Histopathologic type of oral cancer distribution.

Histopathologic type	Number	Percentage (%)
Squamous cell carcinoma	53908	95.7
Non-squamouscell carcinoma	2431	4.3
Total	56339	100

**Treatment methods associated with survival in case of 6830 oral cancer**

There was only 1 article concluded 6830 oral cancer patients with treatment details and survival in total of 27 full articles. 6830 patients with stage I or stage II oral cancer were treated with surgery. Survival rate of 5 years of 6830 patients was 69.7%. 5-year survival rates of 3298 patients treated with neck dissection (71.7%) were higher than 3448 patients without neck dissection (68.0%), P=0.001. However, 5-year survival rates of 1231 patients treated with radiation therapy (57.5%) were lower than 5468 patients without radiation therapy (72.7%), P<0.001 and 187 patients with chemotherapy (53.5%) were lower than 6490 patients without chemotherapy (69.0%), P<0.001 (**Table 9**).

**Table 9.** Treatment methods associated with survival in case of 6830 oral cancer.

Treatment methods	Number	5-Year Survival (%)	P Value
<b>Surgery Neck dissection</b>			
Yes	6830	69.7	P=0.001
Yes	3298	71.7	
No	3448	68	
<b>Radiation therapy</b>			
Yes	1231	57.5	P<0.001
No	5468	72.7	
<b>Chemotherapy</b>			
Yes	187	53.5	P<0.001
No	6490	69	

**Notes:** 84 patients didn't know whether or not got neck dissection, 131 patients were unknown with radiation and 153 patients were unknown with chemotherapy

## DISCUSSION

As other tumors, the incidence of oral cancer has increased with change of environment, habits and diets. But the reports of oral cancer were not as much as lung cancer, liver cancer, breast cancer and so on. We performed the analysis to attract scholars' attention and discuss the incidence of oral cancer.

Of a total of 27 eligible literatures, 10 literatures in Asia, 6 in Europe, 1 in Oceania, 6 in North America and 4 in South America. In this study, North America had the most oral cancer patients because of a great number of cases in North America literatures. Although there was only one document, Oceania was the second most widely distributed region in this research with a large number of cases included. Europe had the third largest number of cases. Asia had the most literatures, but a small number of cases in each document. South America had the smallest number of cases. No literature in Africa was included in the study.

In this study, tongue was still the main site of oral cancer and the most sites in Asia, Europe, North America and South America. This may be associated with the function and mucosa structure of tongue. The tongue was so active that it was easily stimulated by damage, food and mechanical friction. The process of tongue epithelial cell damage and repair lead to cancer by repeatedly injury and stimulation. It was reported that tongue cancer was associated with long-term stimulation of residual roots, dental cusp and bad prosthesis. Tongue was easily injured with friction in these sites, led to traumatic ulcer and cancer under long-term stimulation [32]. Rich blood vessels and lymphatic were found in tongue ventral and dorsal mucosa, submucosa and muscular layer from study on structural characteristics of tongue mucosa. Tumor cells were easy to metastasize with epithelial canceration [33].

Although the specific cause of oral cancer was not clear, most scholars believed that drinking and smoking were closely related to oral cancer. Nicotine of tobacco and alcohol were associated with cancer and included in cancerogenic substances. Studies have shown that smoking could cause DNA damage of oral mucosa cells contacted with tobacco [34]. The double stimulation of high-temperature and carcinogenic substances were easily lead to oral mucosa canceration. Alcohol carcinogenesis was not clear, it may serve as a solvent to promote the absorption of carcinogens, or damaged the cell membrane directly. Acetaldehyde and protein of ethanol metabolism could combine with DNA and induce gene mutation and canceration [35]. In this study, Europe and North America had a large proportion of oral cancer, on the one hand was a large number of people smoked and drank in Europe and North America, on the other hand was more research of scholars in European and North America than others.

People in Southeast Asia not only smoked and drank, but also chewed betel nut. It was reported that [36,37] betel nut chewing was one of the etiological factors of oral cancer. Betel nut was also a pathogenic factor of oral leukoplakia [38]. Betel nut was the fourth most abused substance by humans, containing a variety of cytotoxic and carcinogenic substances. Using tobacco and betel nut at the same time would increase the risk of oral cancer. Studies have found that mechanical stimulation on the oral mucosa by chewing betel nut could lead to mucosal damage and promote the absorption of toxic substances. Arecoline (ARC), tannin, areca-specific nitrosamines (ASNA) and reactive oxygen species (ROS) were the most common components of betel nut in different regions of the world. As a main active substance of betel nut, ARC inhibited expression of p53, p21 and other repair genes on DNA, caused chromosomal variation, regulated cytokine secretion and led to decrease of immune function. The carcinogenesis mechanism of tannin may be associated with ROS produced by its automatic oxidation. ASNA was produced by nitrosylation of ARC in the mouth, could lead to DNA methylation and cause gene mutation inducing tumors. ROS was produced in the process of chewing betel nut, caused changes of oral mucosal structure, made the penetration of toxic substances more easily. ROS also participated in immunosuppression, mediated the toxic effects of ARC through oxidative stress. In addition, betel nut containing lime will promote the oxidation of ROS reaction, resulting in direct damage to the mucosa. Besides, betel nut with lime would promote the oxidation reaction of ROS, causing direct damage to the mucosa. The extractive from betel nut

could stimulate the secretion of transforming growth factor- $\beta$  (TGF- $\beta$ ), endothelin-1 (ET-1), platelet derived growth factor (PDGF), tumor necrosis factor (TNF- $\alpha$ ) and a series of fibrosis-related cell growth factors by oral keratinocytes (KC). These cytokines could promote the proliferation of fibroblasts (FB), oral submucous fibrosis and canceration [39-42].

In this study, an Australian literature from Oceania showed a high rate of lip cancer, probably due to smoking and ultraviolet (UV) radiation. Australian residents at low latitudes enjoyed sun bath and exposure to UV radiation, led to a high incidence of lip cancer [43].

Of the 231,688 patients in this study, the proportion of males in oral cancer was higher than females, without difference in regions and sites. Because more males enjoyed smoking, drinking and chewing betel nut than females. Males were engaged in outdoor physical labor, with more radiation and environmental pollution, which increased the risk of oral cancer.

At the aspect of age distribution, people older than 40 years were more likely to smoke, drink, chew betel nut, be stimulated by UV radiation and environmental pollution, with more denture and lower immune function, so that they were susceptible to viral and fungal infections, leading to the increase of oral disease incidence.

There was only 1 article concluded 6830 oral cancer patients with treatment details and survival in total of 27 full articles. this study indicated that surgery was effective for 6830 patients diagnosed as stage I or II oral cancer. Neck dissection was associated with improved 5-year survival while radiation therapy and chemotherapy were associated with reduced 5-year survival. Patients in early oral cancer could get good prognosis even if they didn't take radiation therapy or chemotherapy. The article only indicated survival at 5 years without survival at more years. In total 6830 patients, only 1231 patients got radiation therapy and 187 got chemotherapy. The sample sizes were too small to indicate the association between radiation therapy or chemotherapy and survival. The research could help us to choose treatments of oral cancer, but still need more study to demonstrate.

## **CONCLUSION**

Human life style changed with the influence of human activities and geographical changes for decades. But the epidemiology of oral cancer didn't change obviously. This study indicated that the tongue was the most frequent site of oral cancer. The most common region was in North America. The tongue was the most reported site in Asia, Europe, North America and South America, while the lip was most common location in Oceania. More males were affected by oral cancer than females. Squamous cell carcinoma was the most common type of oral cancer. Most of oral cancer patients were older than 40 years. Surgery was an effective treatment of oral cancer, but the effect of radiation therapy and chemotherapy still need to be demonstrated.

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