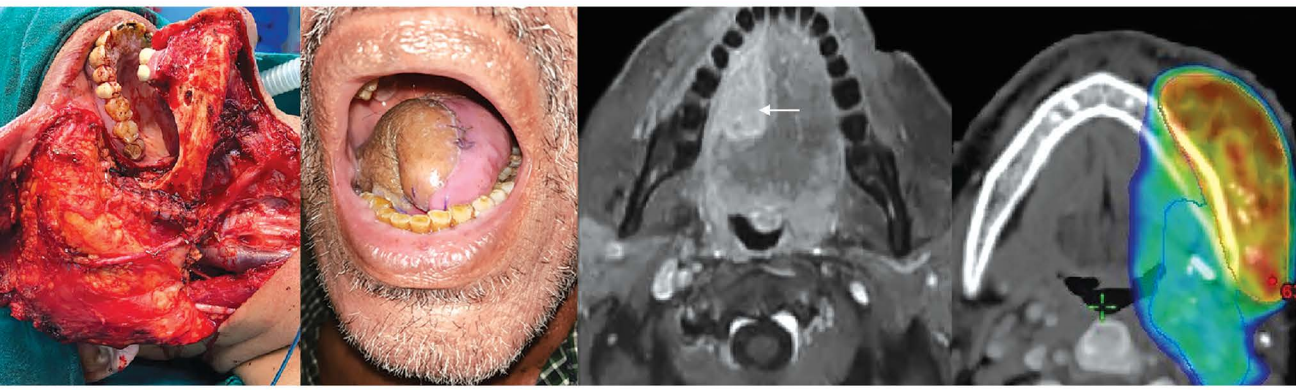
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# *Essentials of*
# Oral Cancer



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*Foreword*
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JAYPEE

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CHAPTER

# 2

# Epidemiology and Etiology of Oral Cancer

*Abhishek Singh, Mudit Agarwal*

## INTRODUCTION

Cancer of the oral cavity is today a major health problem all over the world due to its high morbidity and mortality. There are variations in the prevalence of this cancer in different parts of the world by as much as 20-fold among different countries, age groups, gender, races, and ethnicity. Globally, the incidence of oral cancer has been found to be higher in males than in females, and this risk increases with age. In 2013, oral cancer ranked 11th amongst all sites of cancer. The Indian subcontinent accounts for one-third of the entire oral cancer burden of the globe.

Squamous cell carcinoma is the most common histology to be diagnosed in oral and oropharynx accounting for 90% of oral and oropharyngeal malignancies.

## INCIDENCE AND MORTALITY

The World Health Organization (WHO) in 2015 estimated cancer to be the first or second leading cause of death before the age of 70 years in 91 of 172 countries.

The mortality estimates in 2012 include an age-standardized rate (World) [ASR (W)] of 2.7 per 100,000 for oral and oropharyngeal cancers.

Indian statistics according to GLOBOCAN 2018 **(Fig. 1 and Table 1)**:

- Overall cancer statistics in India (GLOBOCAN 2018):
  - *Number of people estimated to be living with the disease*: Around 2.25 million
  - *New cancer patients registered each year*: Over 1,157,294
  - *Cancer-related deaths*: 784,821
  - Risk of developing cancer before the age of 75 years
    - *Male*: 9.81%
    - *Female*: 9.42%
  - *Cancer-related deaths in 2018*: 784,821
    - *Men*: 413,519
    - *Women*: 371,302
- Risk of dying from cancer before the age of 75 years is 7.34% in males and 6.28% in females.
- Over 200,000 cases of head and neck (H and N) cancers occur each year in India and nearly 80,000 oral cancers are diagnosed every year (2015).
- *India fact sheet*: GLOBOCAN 2018—huge increase in cancer of the lip and oral cavity—114.2% with 56,000 cases in 2012 to 119,992 in 2018.
- Population-based *5-year survival* for patients with oral cavity cancers—*approximately 50% in US, 45–49% in Europe, and approximately 30% in India*.
- 5-year survival rarely exceeds 40% for patients with regional disease and 15% for those with distant metastasis.

Although not listed among the top 10 cancers, some cancers are important within a particular regions or country.

- Cancers of the lip and oral cavity are common in Southern Asia (e.g., India and Sri Lanka) and in the Pacific Islands (Papua New Guinea, has the world's highest incidence rate in both sexes) **(Fig. 2)**.

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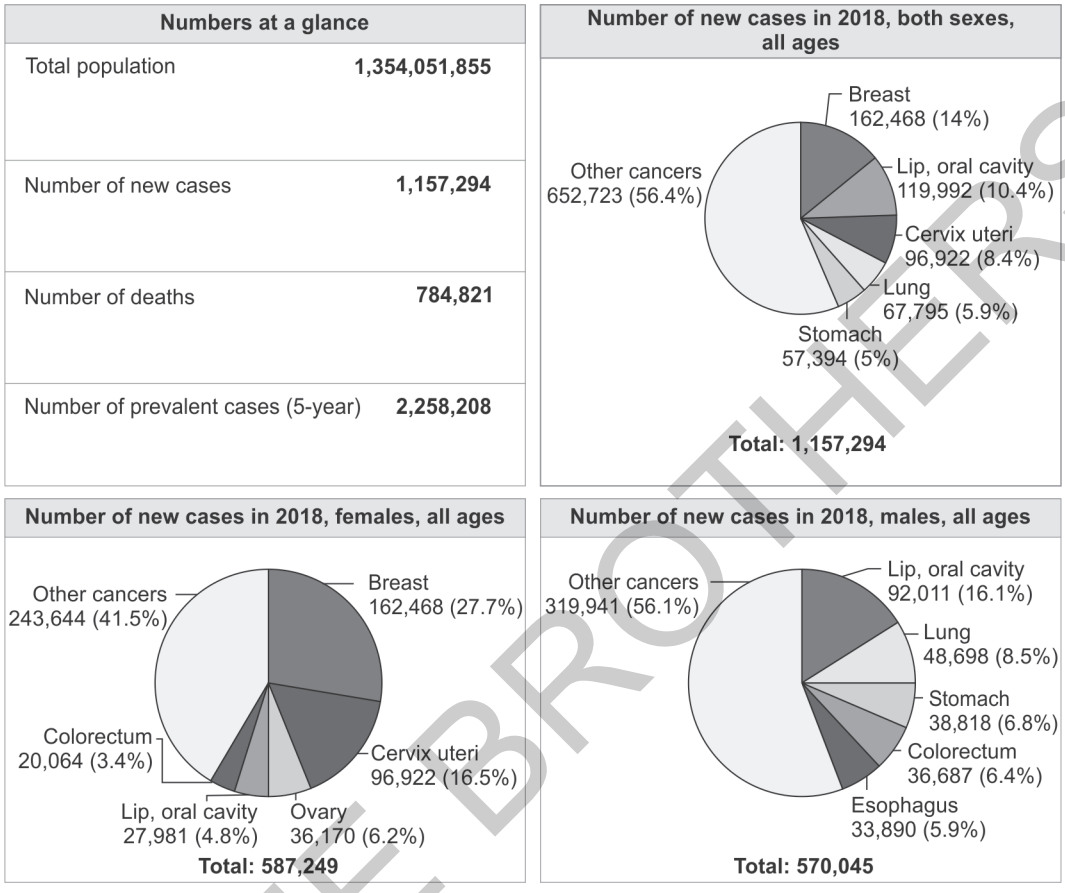



**Fig. 1:** GLOBOCAN 2018.

**TABLE 1:** GLOBOCAN 2018 data (India).

| *Summary statistic 2018* | | | |
|---|---|---|---|
| | ***Males*** | ***Females*** | ***Both sexes*** |
| Population | 701,546,980 | 652,504,878 | 1,354,051,855 |
| Number of new cancer cases | 570,045 | 587,249 | 1,157,294 |
| Age-standardized incidence rate (world) | 89.8 | 90.0 | 89.4 |
| Risk of dying from cancer before the age of 75 years (%) | 7.64 | 6.28 | 6.80 |
| 5-year prevalent cases | 1,000,485 | 1,257,723 | 2,258,208 |
| Top five most frequent cancers excluding nonmelanoma skin cancer (ranked by cases) | Lip, oral cavity | Breast | Breast |
| | Lung | Cervix uteri | Lip, oral cavity |
| | Stomach | Ovary | Cervix uteri |
| | Colorectum | Lip, oral cavity | Lung |
| | Esophagus | Colorectum | Stomach |

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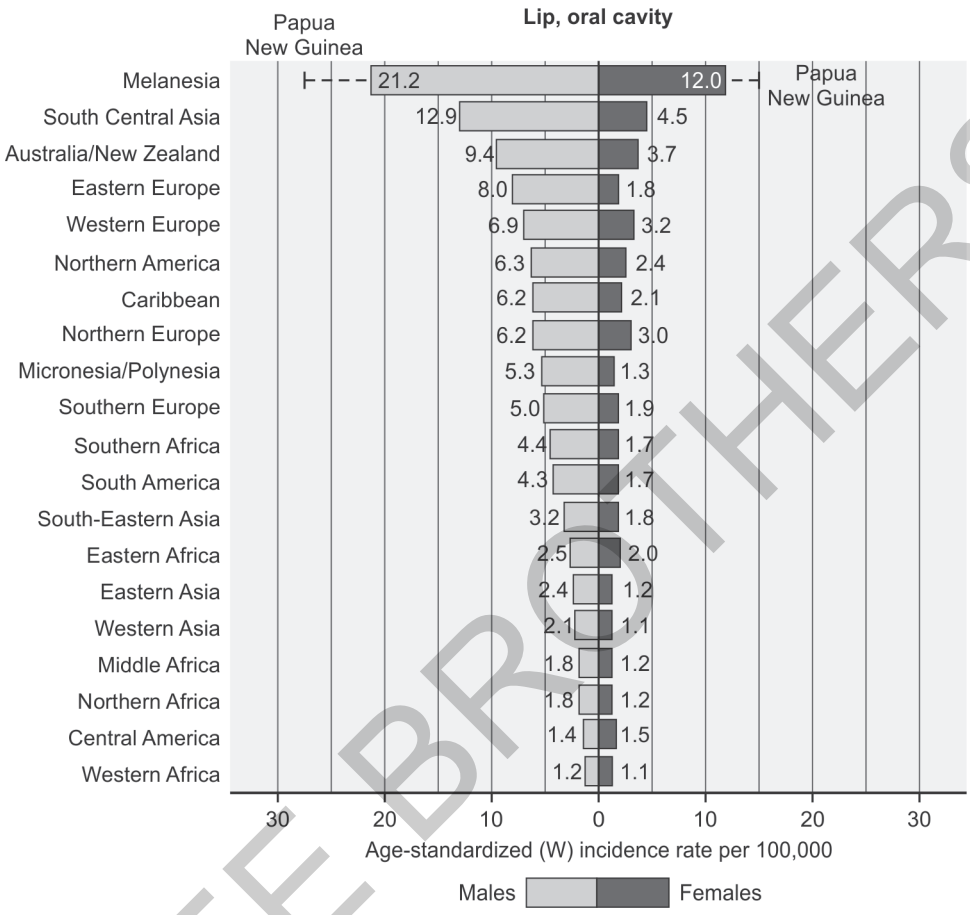



**Fig. 2:** Bar chart of region-specific incidence age-standardized rates by sex for cancers of lip and oral cavity in 2018.
*Note*: Rates are shown in descending order of the World (W) age-standardized rate among men, and the highest national rates among men and women are superimposed.
*Source*: GLOBOCAN 2018.

- It is also the most frequently encountered cause of cancer death among men in India and Sri Lanka.

The Global Initiative for Cancer Registry Development, an initiative of the major cancer organizations, is endeavoring to address inequities in the availability of robust data of incidence of cancer, by increasing its quality, comparability, and use. There are six International Agency for Research on Cancer (IARC) regional centers for cancer registration that have been established to include Africa, Asia, South and Central America, the Caribbean, and the Pacific Islands.

Nair et al., in his review of oral cancers from Regional Cancer Center, Trivandrum, noted that the prevalence of cancer of buccal mucosa was far more than that of tongue cancer (49.9% vs. 23.97%). Younger patients, without a history of smoking or chewing tobacco diagnosed with these cancers, had a worse outcome. Cancers of the gum and alveolar ridge on the contrary is uncommon before the age 50 and affect women more than men.

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**TABLE 2:** Some established cancer registries in India.

| *Zones* | *Registries* | *ASR (male)* | *ASR (female)* |
|---|---|---|---|
| North | Delhi | 123.7 | 135.6 |
| Central | Bhopal | | |
| West | Ahmedabad | 107.2 | 82.9 |
| East | Kolkata | 102.1 | 114.6 |
| South West | Mumbai | 116.3 | 122.4 |
| | Poona | 103.9 | 115.3 |
| | Nagpur | 118.4 | 118.8 |
| South | Madras | 108 | 118 |
| | Trivandrum | 87.8 | 81.1 |
| | Bangalore | 88.3 | 110.7 |
| | Karunagappalli* | 102.6 | 76 |
| Rural | Barshi | | |

*HBCR: hospital-based cancer registry
(ASR: age-standardized rate)

However, according to a study by Shenoi et al. from Maharashtra, mandibular alveolar region was found to be the most common site. Unfortunately >80% of the patients had reported in an advanced stage (Stage III onward).

## Age and Gender

Oral cancer is considered to be a cancer of the elderly. Most of the oral cancers occur between the age of 50 and 75 years. More recently, cancers are being reported in younger patients. A study in Asia found that about 17% of the younger patients are <40 years of age or in the early 40s. Overall, men are more commonly affected than women with a male-to-female (M/F) ratio ranging from 1.45 to 10.5 depending on the geographical region. Japan, for example, has the M/F ratio of oropharyngeal carcinoma as 1.45; similarly, the ratio is 1.5 in Pakistan; 1.9 in Iran; 2.2–2.4 in the United States and 10.5 in Taiwan. However, a reverse gender ratio was seen in Thailand and India (Bangalore) where M/F ratio is 1:1.56 and 1:2.0, respectively.

## Site

It is a known fact the site of occurrence of a particular cancer is determined by the risk factors innate to that particular geographical region. The *tongue* is thus the most common site for oral cancer among Europeans, North Americans and Asians, constituting up to 40–50% of all the oral cancers.

The *buccal mucosa* is the next most common site of oral cancer, seen more in Asian population where areca nut/tobacco chewing is a common habit.

# ETIOLOGY

Studies have reported strong association of oral cancer with the use of *tobacco (smoking* or *chewing)* or *alcohol intake*. According to studies, 57% of all men and 11% of women between the age of 15 and 49 years use some form of tobacco.

Use of smokeless tobacco (SLT) such as betel quid along with smoking is a common practice in many parts of India **(Table 3)**. Betel quid, is commonly known as *paan* which consists of leaf of piper betel vine wrapping

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pieces of areca nut, processed or unprocessed tobacco, aqueous calcium hydroxide (slaked lime). Other forms of tobacco used are, *gutka, zarda, kharra, mawa, and khaini* **(Table 4)**. These are dry mixtures of lime, areca nut flakes, and powdered tobacco.

These days, sachets of premixed areca nut, lime, condiments with or without

**TABLE 3:** Classification of smokeless tobacco products by mode of use.

| *Oral* | | | |
|---|---|---|---|
| ***Sucking*** | ***Chewing*** | ***Other oral use*** | ***Nasal use (sniffing)*** |
| *Chimó* | Betel quid | Creamy stuff | Dry snuff |
| Dry snuff | *Gutka* | *Gudhakhu* | Liquid snuff |
| *Gutka* | *Iqmik* | *Gul* | |
| *Khaini* | *Khaini* | *Mishri* | |
| Loose-leaf | *Khiwam* | Red tooth powder | |
| *Maras* | Loose-leaf | *Tuibur* | |
| *Mishri* | *Mawa* | | |
| Moist snuff | Plug | | |
| *Naswar* | Tobacco chewing | | |
| Plug | Gum | | |
| *Shammah* | Twist or roll | | |
| *Snus* | *Zarda* | | |
| Tobacco tablets | | | |
| *Toombak* | | | |

**TABLE 4:** Some common forms of oral smokeless tobacco and their constituents.

| ***Common/native name*** | ***Ingredients*** | ***Countries/populations*** |
|---|---|---|
| *Toombak* | Sodium carbonate and tobacco (*Toombak*-associated carcinogens have high prevalence of p53 protein aberration) | Sudan |
| *Shammah* | Tobacco, slaked lime, and ash | Saudi Arabia |
| *Naswar* | Tobacco, slaked lime, indigo, cardamom, oil, and menthol | Iran, Afghanistan, Pakistan, Central Asia |
| *Nass* | Tobacco, ash, cotton, and sesame oil | Iran, Afghanistan, Pakistan, Central Asia |
| *Mawa* | Areca nut, lime, and tobacco | India |
| *Gudakhu* | Tobacco and molasses | Central India |
| *Zarda* | Boiled tobacco | India and Arab countries |
| *Paan/betel quid* | Areca nut, betel leaf, slaked lime, spice, and catechu, with or without tobacco | Indian subcontinent, New Guinea, Southeast Asia, and South America |
| *Mishri* | Burned tobacco | India |

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powdered tobacco are available freely and are very popular among old and young alike. The *paan or gutka* is stored in the cheek and chewed or sucked for several minutes, or some users choosing to keep it overnight.

Addiction to tobacco typically starts early in life through company of family member or peers. Various researches carried out across the country indicate that at least a third of school children <15 years of age have used one or another of tobacco. However, with improved public health awareness, the use of tobacco is decreasing everywhere, including India. Recently, increased incidence of oral cancer, especially tongue cancer has been seen among young adults. In a study of 482 consecutive patients of H and N cancer at a tertiary care cancer center in India, 135 out of the 286 (47%) oral cavity cancer patients had no known habit of use of tobacco or alcohol.

Prevalence and pattern of SLT use:

- According to the population-based surveys, on an average currently nearly 25 crore Indians use SLT.
- Prevalence among men is higher, with more than one in every three using tobacco in some or the other form.
- A little over 14 crore men and almost 6 crore women use SLT in India.

More than one in every five urban Indians use tobacco products.

Smokeless tobacco is used commonly in Africa, North America, South-East Asia, Europe, and the Middle East in the following forms:

- Betel quid with tobacco, commonly known as *paan or pan* **(Fig. 3)**. It consists of four main ingredients: (1) betel leaf (leaf of Piper betel vine), (2) areca nut (*Areca catechu*), (3) slaked lime, and (4) tobacco. Tobacco is the most important ingredient.
- *Gutka*: These are sun-dried, roasted, finely chopped tobacco, areca nut, slaked lime, and catechu mixed with some flavorings and sweeteners. It is kept in the mouth, sucked, and chewed.
- *Khaini*: This substance is made from sun-dried or fermented coarsely cut tobacco leaves. The tobacco used for this type is derived from *Nicotiana rustica* and/or *N. tabacum*. Areca nut are often added to khaini during use. It predominantly causes cancer of GBS (*gingivobuccal sulcus*) due to habit of pouching in the inferior GBS.
- *Zarda*: Tobacco, lime, spices and vegetable dyes. Tobacco leaves are broken up and boiled along with lime and spices until dry. This mixture is dried and later colored with vegetable dyes. Zarda is commonly chewed mixed with finely chopped areca nuts and spices. This is frequently used as an ingredient in the betel quid.

Tobacco products for smoking:

- *Cigarette*: This is a roll of tobacco wrapped in paper or any nontobacco material. It may be filter-tipped or untipped, about 8 mm in diameter and 70–120 mm in length.
- *Cigar*: Any roll of tobacco wrapped in leaf tobacco or in any other substance containing tobacco.

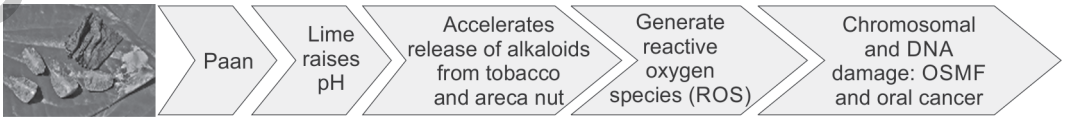



**Fig. 3:** Effects of *paan* consumption.
(OSMF: oral submucous fibrosis)

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*Types*: Little cigars, small cigars ("cigarillos"), regular cigars, premium cigars. Some of the little cigars have filter tips and are shaped like cigarettes. Regular cigars are up to 17 mm in diameter and 110–150 mm in length.

- *Bidi*: Hand-rolled Indian cigarette. These are sun-dried temburni leaf rolled into a conical shape together with flaked tobacco and tied with a thread.
- *Chuttaa*: Hand-rolled cigarette used for reverse smoking. Used commonly by women in India (Rural and tribal—north coastal districts of Andhra Pradesh).

Advances in chemical analytical techniques have identified increasing number of carcinogens in tobacco smoke. The carcinogens identified include 10 species of polynuclear aromatic hydrocarbons (PAHs), six heterocyclic hydrocarbons, four volatile hydrocarbons, three nitrohydrocarbons, four aromatic amines, eight N-heterocyclic amines, 10 N-nitrosamines, two aldehydes, 10 miscellaneous organic compounds, nine inorganic compounds, and three phenolic compounds. Eleven compounds (2-naphthylamine, 4-aminobiphenyl, benzene, vinyl chloride, ethylene oxide, arsenic, beryllium, nickel compounds, chromium, cadmium and polonium-210) classified as IARC Group 1 human carcinogens have been in the smoke.

Since the last IARC Monograph on tobacco smoking (IARC, 1986a), the emphasis of research on carcinogens in tobacco and its smoke has primarily been on the following due to their established carcinogenic potency:

- Benzo[a]pyrene (a surrogate for all PAHs)
- Tobacco-specific N-nitrosamines (TSNA), especially N′-nitrosonornicotine (NNN) and 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK).
- Aromatic amines, especially 4-aminobiphenyl (4-ABP)

**Key Points**

- *Heavy smokers of cigarettes*: 5–25-fold increase for developing oral cancer
- *>1 packet/day*: 13-fold increase for developing oral cancer
- Starting age below 18 years and duration over 35 years are high-risk factors.
- Tobacco contains over 50 known carcinogens.
- The risk of oral cancer is *reduced by 30%* in those who have discontinued its use for *1–9 years* and by *50%* in those who have stopped habit for *>9 years*.
- Pipe and cigar smokers have an increased *risk of oral cancer* compared to other head and neck subsites.
- Reverse smoking is commonly associated with cancer of the hard palate and palatine arch.
- Marijuana smoking is associated with release of carcinogenic agents such as polycyclic aromatic hydrocarbons, benzopyrene, phenols, phytosterols, acids and terpenes. A study from Memorial Sloan Kettering Cancer Center reported an overall risk of 2.6.

## ALCOHOL (FIG. 4)

Alcohol has been implicated in the development of oral cancer. Alcoholic beverages have been reported to be carcinogenic to humans for cancers of the oral cavity, pharynx, larynx, esophagus, and liver but ethanol has not been found carcinogenic in animal studies.

Alcohol acts synergistically with tobacco to increase the risk of development of oral cancer.

A strong dose–response relationship has been observed in most studies. (Relative risks that range from 3.5 to 9.2)

Some substances that are thought to be carcinogenic to humans have also been seen in alcoholic beverages. A few of them are: N-nitroso compounds, mycotoxins, urethane, and inorganic arsenic.

The *major metabolite of alcohol is acetaldehyde*, which is transformed by the enzyme alcohol dehydrogenase (ADH). Acetaldehyde is then oxidized to acetate with

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**Fig. 4:** Mechanism of action of alcohol.

the help of aldehyde dehydrogenase (ALDH). Toxic effects of acetaldehyde may be:

- Acetaldehyde causes damage to the DNA in cultured mammalian cells.
- It interferes with synthesis and repair of DNA.
- Acetaldehyde inhibits the enzyme 6-methyl guanine transferase which is needed for repairing damages caused by alkylating agents.
- Increased accumulation of acetaldehyde in the body whether due to increase in its production or decrease in its elimination, are deleterious.

## HUMAN PAPILLOMAVIRUS

Human papillomavirus (HPV) infects the oral cavity of healthy individuals, and several HPV-related lesions have been described in literature.

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Prevalence of HPV in oral and oropharyngeal squamous cell carcinoma (OSCC) has been reported to be 33.6% in Eastern India, 48% in South India, 15% in West India, 27.5% in Central India, and 28% in Northeast India.

## DIET AND NUTRITION

Fruits and vegetables, particularly carrots, tomatoes, and green vegetables have been proved to reduce risks of oral and pharyngeal cancer. Other *food types that have a protective effect* are fish, cereals, legumes, protein, fat, fresh meat, chicken, liver, shrimp, lobster, vegetable oil, olive oil, bread, and fiber.

Many micronutrients and vitamins also decrease the risk of development of oral cancers. These are vitamins A (retinol), carotenoids (β-carotene), potassium; and selenium. β-carotene, retinol, retinoids, vitamin C (AA), and vitamin E (α-tocopherol), which are antioxidants that are useful in reducing free radical reactions which are responsible for DNA mutations, changes in enzymatic reactions, and lipid peroxidation of cellular membranes.

## OCCUPATIONAL RISK

Exposure to excessive solar radiation/ultraviolet (UV) light are notorious in causing lip cancers. UV rays can also cause actinic cheilitis which may transform later to OSCC.

## GENETIC FACTORS

Some individuals inherit inability to metabolize carcinogens or procarcinogens and/or an impaired ability to repair the DNA damage. Genetic polymorphisms in the genes coding for the enzymes (P450 enzymes and xenobiotics-metabolizing enzymes) that are causative for metabolism of the tobacco carcinogen are believed to play an important role in the genetic predisposition to tobacco-induced head and neck cancers.

## DENTAL FACTORS

Chronic mechanical irritation of the mucosa of the oral cavity can arise due to following:

- Defective teeth (malpositioned with sharp or rough surfaces because of decay or fractures), (1.13 risk).
- Ill-fitting dentures (sharp or rough surfaces, lack of retention, stability, or overextended flanges) (Four-time risk)
- Parafunctional habits (e.g., oral mucosa biting or sucking, tongue interposition, or thrusting).

## SEER 2016 ANALYSIS: LIFETIME RISK OF DEVELOPING CANCER

Based on 2014–2016 data, approximately 1.2% of men and women are likely to be diagnosed with cancers of oral cavity and pharynx at some point during their lifetime.

### Survival (Fig. 5)

The outcome for cancers of the lip, appear to be best, with over 90% of patients surviving for 5 years. But in general, prognosis deteriorates with advanced stage of the disease. For cancers of oral cavity, women have been found to have higher survival rates than men. TNM stage at presentation significantly affects 5-year survival. For mobile tongue, 5-year survival for stage 1 disease is 80%, while, it drops to 15% for stage IV.

Recurrence is often an inevitable aspect of treatment outcome. It indicates poor prognosis. Recurrence may be local, regional, locoregional or distant metastasis. Recurrence rates vary between 25 and 40% after a follow-up period of 2–4 years.

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| | |
|---|---|
| Estimated new cases in 2019 | 53,000 |
| % of all new cancer cases | 3.0% |

| | |
|---|---|
| Estimated deaths in 2019 | 10,860 |
| % of all cancer deaths | 1.8% |

| Percent surviving 5 years |
|---|
| **65.3%** |
| 2009–2015 |



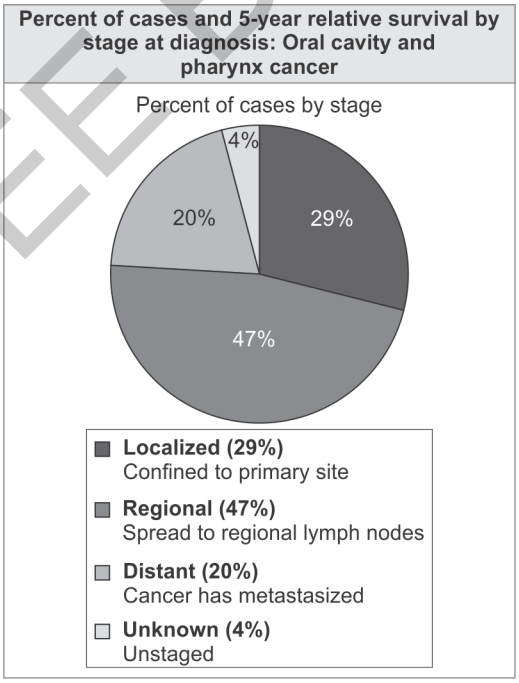




**Fig. 5:** Survival by stage.

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## Mortality

For most countries age-adjusted death rates from oral cancer have been estimated to be 3–4 per 100,000 men and 1.5–2.0 per 100,000 for women. Globally a low 5-year survival rate of 50% is seen among patients with oral cancer.

**KEY POINTS**

- Squamous cell carcinoma is the most common type of malignancy that is diagnosed in the oral and oropharyngeal regions.
- *India fact sheet*: GLOBOCAN 2018, cancer of the lip and oral cavity, huge increase of 114.2% with 56,000 cases in 2012 that increased to 119,992 in 2018.
- Population-based *5-year survival* for patients with the group of oral cavity cancers—*approximately 50% in US, ranges from 45 to 49% in Europe and approximately 30% in India.*
- *RCC, Trivandrum*: Highest prevalence of cancer of buccal mucosa (49.9%).
- Maharashtra has reported mandibular alveolus as the most common site of oral cancer.
- Estimates indicate 57% of all men and 11% of women between 15 and 49 years of age use some form of tobacco.
- 14 crore men and almost 6 crore women use SLT in India.
- *Heavy smokers of cigarettes*: 5–25-fold increase for developing oral cancer.
- *>1 packet/day*: 13-fold increase for developing oral cancer.
- *Other etiological factors*: Alcohol, genetic, diet and nutrition, occupation, and dental factors.

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# *Essentials of*
# Oral Cancer

The knowledge about head and neck cancers has undergone exponential growth over last three decades. Clinicians keep struggling to collect information so as to help them in decision-making in oral cancer management. In this book, we have selected key materials based on the combined wisdom and surgical expertise of an impressively well-informed institutional team. We regard it as a great pleasure and privilege to have been associated with such a wonderful team.

We hope that in its current form, the book will continue to be a major resource not only for trainees but also for established practitioners in otolaryngology, maxillofacial surgery, plastic surgery, and clinical oncology whose specific work includes a major head and neck practice. This book is in the form of tips and tricks for all oral cancer clinicians, not giving any details or trials or studies or references.

This book is one-stop-shop for non-specialists and Head and Neck Specialists to keep abreast with oncological principles from "Prevention to Palliation". It will be particularly useful for postgraduates who wish to pursue career in oncology. Internists and general practitioner will find this a useful resource in their day-to-day practice. This book is a joy to own, a pleasure to read and, above all, a powerful force to advance treatment standards in the huge variety of oral conditions.

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