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ORAL CANCER AND ITS EPIDEMIOLOGY, THERAPY AND RISK FACTORS, CASE STUDIES IN KARNATAKA: A REVIEW

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ABSTRACT: Oral cancer is one of the lethal cancers, having first rank in India and sixth most deadly cancer in world and most of the time occurs due to improper lifestyle and adverse habits. Cancers of the lung, oral cavity, pharynx, larynx, esophagus, urinary bladder, renal, pelvic and pancreas are among the neoplastic diseases induced by smoking. Epidemiological studies have firmly identified the connection between smoking and oral cancer. In the review, we have discussed about the risk factor of oral cancer, recent advancement in treatment of oral cancer and cases in Karnataka state of India. We focused on the reason of oral cancer, as many studies suggested that tobacco (smokeless and smoking), excessive consumption of alcohol, and exposure of radiation are the main causing agents of oral cancer. People adopted tobacco socially in India and there is something to worry about that people are not aware that tobacco is primary causal factor of oral cancer. In present study, we focused on the treatment of oral cancer and what modification in DNA can lead the oral cancer and how to reverse the action of the cancerous cells to prevent the cancer.

INTRODUCTION: Oral cancer has been attributed to being one of the most challenging and relevant form of cancer incidences. Despite enhanced prognosis and progress in therapy and research, the survival of Oral Cancer patients has still not significantly improved. Thus, this poses a severe challenge for the research related to biomedical sciences.

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This paper targets to cover vital aspects of this particular cancer, underlying, histological, clinical, and molecular notes for a clearer picture of their biological framework. This would thus allow researchers to create a blueprint that could assist in bettering the patients with a superior prognosis. According to some research approximately two lakh people deceased yearly worldwide and about 46 thousand die in India by oral cancer [1]. Some studies suggest a significant difference in the rate of mouth cancer in various areas of the world.

Oral cancer is the sixth most common cancer in the world. In Southeast Asia, oral cancer is the second most common cancer and second common cause of cancer death among males.

One-third case of global oral cancer and one-half of global mortality from oral cancer are described from Southeast Asia. Persons exposed to smoking, drinking, and betel quid chewing together are at high risk compared to individuals exposed to any one of these factors [2]. In Southeast Asia, most cases of OSCC happen in the buccal and esophagus areas of the oral cavity [3]. Oral cancer is considered one of the major health issues in the entire Indian subcontinent and is ranked third among the all kinds of cancer in the country**.**

Around 20 per 100,000 population, one that accounts for about 30% of all cancers in India are patients suffering from oral cancer [4, 5]. The incidence difference of the disease and the pattern can be attributed to the demography of the region, along with prevalence difference in the regions because of disease-specific risk features [6]. It is one of the highest concerning diseases in the country. First of all, later-stage diagnosis, resulting in poor treatment and cost burden to the patients below the poverty line [7]. Moreover, there is limited health service in middle- and low-income countries and to trained providers [8]. Earlier detection bids the best chance for a better and longer survival rate and improves treatment results and affordable healthcare [9]. Thirdly, people of lower socioeconomic groups affected more by oral cancer because of more introduction to risk factors like tobacco, betel nut, *etc* [10]. Lastly, the common cases presented to a healthcare center are way at advanced stages of cancer, and the chances of survival are minimum by then [11]. Profound knowledge on the matter, aetiology and risk factors are the ways to curb the growth of oral cancer.

1. Definition and Illustrations: Oral cancer is a neoplasia of the malignant nature, one that arises on the oral cavity or the lip. Oral cancer is predominantly known as squamous cell carcinoma (OSCC). This is because around the dental area, almost 90% of the cancers originate histologically in the squamous cell lining [12, 13]. There are various stages of differentiation, along with a tendency to metastasize into the lymph node [14]. The occurrence of OSCCs differs in various parts of the world and it is noticed that exposure to risk factor is also differ [15]. A quantitative study of any disease depends on specific and constant definitions. This also stands true for cancer epidemiology, which includes explanations of topography, histo-pathology and tumour performance. In case of oral cancer, variations prevail in the anatomical subsites involved in both oral cavity and oropharynx groupings. Therefore, oral cancer is progressively being recognized as part of two different diseases: oral cavity cancer (OCC), also known as 'mouth cancer' and oropharyngeal cancer (OPP), also known as 'throat cancer'.

Incidence rates the best measure the incidence (risk) burden of cancer in a population. Cancer incidence rates are the number of new cases diagnosed in the population over a given period (usually a year) expressed as a rate by dividing this by the total population at risk during that period (denominator). The denominator is usually adjusted to account for different age profiles in different populations referenced to a standard population, which has a known population age-structure – this is often the European Standard Population, which is a theoretical population adding up to a total of 100,000 persons.

Given the relatively low volume of oral cancer and the long lag-time between exposure to risk factors and cancer diagnosis, case-control study designs are the mainstay of epidemiological investigations. In such case-control studies, a group of patients with oral cancer ('cases') and a comparable group of study participants without oral cancer ('controls') are recruited. Information on their histories of exposure to risk factors is collected and compared. The epidemiology of the cancer sheds light into an interesting fact that among ethnic groups, this cancer is prevalent more in men than in women [http://seer.cancer.gov/statfacts/html/oral cav.html]. In worldwide reports, cancers of all regions of the oral cavity and pharynx are grouped and collectively represent the sixth most common cancer in the world.

The most common symptoms of oral cancer are as follows: it is seen in an oral cancer patient that they have swellings or thickenings, lumps, crusts on the lips and gums inside the mouth. Even the texture of teeth changes due to oral cancer. Sometimes red or white patches develop inside the mouth, and they bleed. The oral cancer causes loss of feeling or numbness but sometimes it is also seen that it pains in the area of mouth. While some patients feel

persistent sores on the neck and mouth that bleed, and the wounds do not heal quickly. Even a sore throat becomes chronic which results in hoarseness and a change in voice. Oral cancer patients have difficulty swallowing and chewing, speaking, and moving the jaw and tongue. Ear pain and dramatic weight loss are also symptoms of oral cancer.

2. Causing Agents: Oral cancer is noticed different part of the oral cavity like lips, tongue, salivary glands, soft palate and oropharynx. Multiple studies suggest that oral cancer-causing agents contain dietary factors, smokeless tobacco chewing (Gutka, Pan *etc*.), tobacco smoking (Beedi, Cigarette etc), alcohol drinking, Human Papilloma Virus (HPV) infections and exposure to carcinogenic agents [16]. Oral cancer is the most common cancer in India amongst men (16.1% of all cancers) and second most common cancer in amongst women (10.4% of all cancer). According to a survey, due to tobacco use, mortality is estimated at upwards of 3.5 thousand persons per day. The *"India Against Cancer"* works against cancer in India, which is run under the doctors and researchers at the National Institute of Cancer Prevention and Research (NICPR), a premier institute under the Indian Council of Medical Research (ICMR).

According to "India Against Cancer", due to tobacco (smoked and smokeless), approximately 3,17,928 deaths (men and women) were recorded in 2018 in India. It is reported (Consolidated report of hospital-based cancer registries 2007-2011, National Cancer Registry Programme (ICMR), Bangalore) that tobacco contribute in oral cancer about 80-90% of all cancer.

Vishma *et al.*, reported in her studies that she collected 479 sample of oral cancer from Mandaya, Karnataka[17]. She reported that 36.7% of the total oral patients supposed that oral cancer can be prevented by treatment, 41.8% believed that it can be treated, 35.1% of the patients supposed that oral cancer is increased with the age, while 18.6% patients think that oral cancer is infectious. In the similar study conducted in Gorakhpur, Uttar Pradesh[18] it is noticed that 74.1% of the total patients said that oral cancer is curable, 40.9% did not agreed with risk for oral cancer increases with the age, where 10.8% believed that oral cancer is infectious.

Survey was conducted in rural Bangalore and mentioned in his paper that only 19.28% of the total patients thought that oral cancer is preventable [19].

The most common symptoms are ulcer and lump in the mouth mentioned that in their studies that 40% of the total (479) respondents did not know the oral cancer's symptoms. In different studies conducted in Gorakhpur (40%), Portugal (10%), Chennai (31.7%), and Turkey (20.8%) of the patients did not know about the common symptoms of oral cancer. Only 8.1% of the responders believed that smokeless tobacco is the causing agent, only 0.8% of the total responders thought that smoking is the factor for oral cancer, while 43% of the responders knew that more than three (chewing of tobacco, smoking and alcohol consumption, *etc*.) causing agents of oral cancer. A study suggested that around 90% of the total responders believed that smokeless tobacco is a risk factor of oral cancer and 75.4% patients believed that smoking is risk factors for oral cancer. According to monteiro [20, 21, 22] studies that 89.5% of the responders believed that tobacco (89.5%) is risk factor for oral cancer and 32.3% responders said that alcohol is risk factor for oral cancer.

Sathyanarayana *et al.,* [23] found that with regard to risk factors, 50% of the respondents knew that cigarette smoking was a risk factor for oral cancer. Other Risk factors for the growth of oral cancer includes, smoked tobacco (cigarette, cigar, and pipe) people have 6 times more cancer than the non-smoker people. Smokeless tobacco (snuff, dip, and chewing tobacco) users are 50 times more likely to develop cancers of the cheek, gums and lining of the lips. Excessive consumption of alcohol is also a high-risk factor of oral cancer which causes 6 time more in drinker then non-drinker. It is also reported that who has family history of oral cancer, is at high risk of cancer. The human papillomavirus (HPV) also causes oral cancer. To avoid oral cancer, self-examination should be conducted at least once in a month. If any lumps are presented in the area of the mouth, then should consult with a dentist. The American Cancer Society mentioned oral cancer screening tests should be done in every 3 years who over age 20 and annually for those who over age 40.

3. Tobacco: In the year 2007, IARC decided "there is quite an evidence to establish that snuff smoke is carcinogenic, and for example, it causes cancer of the oral cavity and pancreas" (World Health Organization, 2007) [24]. Risk for oral cancer is 3 times more in smokers as compared to nonsmokers [25]. Immunity weakens in case of Cigarette smoking in the oral cavity because of the risk of periodontitis, gingivitis, oral cancer [26]. It contains various elements enhancing cancer that are mostly: nitrosamines, benzopyrenes, and aromatic amines. Such chemicals are termed pre-carcinogens that must go through coordinated alterations triggered by oxidative enzymes. The final product thus becomes depleted of electrons to be covalently bound to the DNA. This generates an adduct mutated area, free radicals, with unpaired electrons make them reactive and are being capable of enhancing mutations by complex mechanisms [27].

India is known as a global capital for smokeless tobacco because, according to the Global Adult Tobacco Survey- 2010, smokeless tobacco is consumed by more than one-third (35%) adult population in India. Therefore, it is a common community health problem in India. Out of 35% population, 21% are used only smokeless tobacco products, while 9% are used only smoking, and 5% adult population are addicted to both smokeless and smoking tobacco products (GATS India 2009-2010) [28]. 20.6% of the adult population is addicted in the United States of America. In western countries, smokeless tobacco use is similar to India. According to World Health Organization, tobacco use is high risk factor for oral cancer which is responsible for 22% of cancer death in over the world. According to the International Agency for research on cancer (IARC), smokeless tobacco is associated with oral cancer only. Gajalakshmi *et al.,* [29] reported in his paper that due to oral cancer, the death rate has increased by 5times in smokeless tobacco users than non-tobacco users. The larynx, pharynx, esophagus, cervix, and stomach were also found among the smokeless tobacco users.

4. Alcohol: Alcohol is both considered a local and systemic risk factor. This is seen as augmented permeability of mucosa in the oral region, epithelial lipid dissolving that causes epithelial atrophy and DNA synthesis interference. It also has genotoxicity and mutagenic effects that cause low salivary flow. It affects the ability of the liver to deal with carcinogenic compounds. Their chronic use is associated with damage of immunity that results in increased probability of infections and neoplasms [30].

5. Other Factors: Human papillomavirus is mainly linked with the carcinoma of the oropharynx [31] along with ultraviolet radiation (UV). HPV18 is a possible cause of oral cancer [32]. HPV-related head and neck squamous cell carcinoma (HNSCC) common sites are tonsils and the base of the tongue inside the oropharynx. The presence of HPV is an established prognostic biomarker of favorable out-come in locally advanced oropharyngeal cancers [33]. HPV contributes to carcinogenesis with the help of two virus-encoded proteins: E6 protein p53 tumor suppressor gene degradation; E7 tumor suppressor gene pRb degradation (retinoblastoma protein) [34], leading to an inhibitor overexpression of cyclin-dependent kinase. UVB also causes `lip cancer.

6. Tumor Microenvironment (TME): The Tumor Microenvironment (TME) of OSCC includes immune cells, cancer-associated fibroblasts (CAFs). Oncogenic changes regarding gene expressions lead to microenvironmental changes such as overproduction of cytokines, ROS accumulation, epithelial-mesenchymal transition.

The immune response in OSCC is suppressed by induced apoptosis by T cells, overexpression of cytokines, and alterations in antigen processing machinery [35]. Transforming growth factor-β (TGF-β) offers to EMT and immunosuppression, along with the evolution of CAFs. OSCC uses the glyco-lytic and oxidative metabolism to feed tumor genesis through mechanisms which are coupled between regions of cancer cell (parenchyma) and TME cells (stroma) [36.]

7. Case in Karnataka: Reasons for Late Diagnosis: A study on oral cancer was conducted based on hospital records by Karnataka Cancer Treatment and Research Centre (KCTRI), Karnataka, India Priyadarshini selected 1113 oral cancer patients, who were registered in hospital between January, 2001 to December, 2005 for the treatment for oral cancer [37]. This study suggested that North Karnataka people did not become aware of the reason for oral cancer. The study was done

on the basis of socio-economic status of oral cancer patients, she selected from three different regions of Karnataka-rural, urban and semi-urban. Almost 98% of the patients used tobacco, betel nut *etc*., which habit tobacco chewing habit was significantly higher ($p<0.001$) compared to other habits of patients. Approximately 33.5% of the patients were suffered from buccal mucosa carcinoma and 28.5% of the patients were suffered with tongue carcinoma. It is also reported in some literature that tongue carcinoma was most common site for oral cancer after the buccal mucosa carcinoma [38, 39, 40].

De Vita discussed the reason for oral cancer; tobacco, alcohol, and radiation exposure are the most general risk factor for the occurrence of oral cancer [41]. Prolonged oral cancer can cause death [42, 43]. The cancer patients in South Karnataka based on their type of cancer, patient's age, lifestyles, and diabetes. It is reported that glucose inhibits DNA synthesis in cultured hepatocytes, a prerequisite for cellular proliferation [44.] Hence diabetics should show a certain amount of immunity against cellular proliferative diseases like cancer [45, 46].

The Kasturba Medical Hospital, Mangalore, Karnataka treats cancer patients since the year 1999. Itagappa *et al*., [47] chose Kasturba Medical Hospital and took 400 cancer patients for his studies. 25.5% patients out of 400 cancer patients were observed with oral cancer, shown in **Table 1**. Ghose *et al.,* [48] reported that tobacco is the primary causal agent for oral cancer in Indian subcontinent. Itagappa *et al*., reported that 28.4% of the total oral cancer patients were addicted to tobacco, and 64.7% of patients did not have addiction to alcohol, while only 6.9% of the total patients did not have any addiction history, shown in **Table 2**. In the ICMR report written by Ramachandran *et al*., 48% of male oral cancer patients and 20% of female oral cancer patients were addicted to tobacco in India [49]. However, these reports indicate that oral cancer is higher in both sexes (male and female) than the other type of cancer. Excessive use of tobacco is a known primary causing agent for oral cancer in South Karnataka, India. Mukherjee *et al*. reported that tobacco products (Pan and gutka, *etc*.) chewing is a socially accepted practice among both sexes (male and female) in many regions of India [50].

TABLE 1: TYPE OF TUMOUR DISTRIBUTION AND SEGREGATION OF DIABETICS AND NON-DIABETICS

S. no.	Tumour	No of cases (n)	% of cases	Diabetic cases	Non-Diabetic cases
1	Oral	102	25.5	2.0	100
2	Breast	73	18.2	1.0	72
3	Cervix	73	18.2	3.0	70
4	Non- Hodgkins Lymphoma	25	6.2	-	25
5	Oesophagus	24	6.0	-	24
6	Ovary	19	4.7	2.0	17
7	Lung	11	2.7	-	11
8	Leukemia	10	2.5	-	10
9	Brain	9	2.3	-	09
10	Parotid	8	2.0	1.0	07
11	G.I.T.	8	2.0	1.0	08
12	Uterine	7	1.7	-	06
13	Multiple Myeloma	6	1.5	-	06
14	Liver	5	1.3	-	05
15	Thyroid	5	1.3	-	05
16	Kidney	4	1.0	-	04
17	Lymphoma	3	0.8	-	03
18	Prostate	3	0.8	-	03
19	Bladder	2	0.5	-	02
20	Vagina	2	0.5	-	02
21	Testis	1	0.3	-	01
	Total	400	100	10	390

Note: This table has been adopted from the Itagappa and Rao, 2004.

TABLE 2: DISTRIBUTION % OF TUMOUR CASES AS PER PATIENTS' ADDICTIVE HABITS

S. no.	Tumour	Tobacco user	Tobacco and alcohol user	No addiction
1	Oral	64.7	28.4	6.9
2	Breast	26	-	74.0
3	Cervix	38.4	-	61.6

4	Non- Hodgkins Lymphoma	32	8	60
5	Oesophagus	41.7	45.8	12.5
6	Ovary	21.1	-	78.9
7	Lung	27.3	63.6	9.1
8	Leukemia	10	-	90
9	Brain	22.2	11	66.7
10	Parotid	37.5	50	12.5
11	G.I.T.	-	50	50
12	Uterine	14.3	-	85.7
13	Multiple Myeloma	16.7	50	33.3
14	Liver	-	60	40
15	Thyroid	-	20	80
16	Kidney	25	25	50
17	Lymphoma	66.7	-	33.3
18	Prostate	33.3	66.7	-
19	Bladder	50	50	-
20	Vagina	100	-	-
21	Testis	-	-	100
	Total	400	100	10

Note: No patients were found with alcohol addiction

There is a wide variable rate in the incidence of oral cancers in India; she recorded that oral cancer was established in all cancers, approximately 12% in men and around 8% in women. In oral cancer, the rate of survival is very less approximately 50%. But early diagnosis of oral cancer rises the chances of patient's survival. Mouth is easily accessible for medical examination and self-examination.

Lack of information about the causes of oral cancer, their signs, and symptoms among the population are the common reasons for diagnosis at an advanced level. Moreover, if the patients know the risk factor for oral cancer, then it could be preventable or controllable [51]. Gopinath noticed that rural people have not enough knowledge about oral cancer and its causes and preventions compared to urban people [52]. This data was taken by Gopinath and his colleagues, as he collected data from the rural area of Dakshina Kannada district of Karnataka in October 2014 with the help of a questionnaire. In that survey, they took data of 267 people with the age group 12-80 years who came looking for dental treatment at Nitte University, Karnataka [53].

According to Gopinath, 13.1% people out of 267 people did not hear about the oral cancer, 4.9% people believed that oral cancer caused by hereditary, and some people believed it spreads by sexual and blood transfusion. While 6.7% of people said that sharing clothes and utensils are a major reason for oral cancer. Ramachandra also explained in his article that illiteracy is a common cause for increasing oral cancer incidences along with chewing habits. Rural patients were also confused with the question regarding oral cancer in AIDS patients [54]. 3.4% of patients believed that most oral cancer is seen in HIV-positive patients. Argerak is expressed concern about psychosocial thoughts for the post-treatment of head and neck cancer patients. Ariyawardana's survey revealed that 5.9% of the population was not aware of treatment possibilities, and 5.4% believed that there is no treatment available for oral cancer [55]. This may lead to a "loss of hope" type of situation, resulting in a delay in seeking treatment, or the patient may not seek treatment. Das expressed concern in his article about increase the awareness for health education and cancer prevention [56].

8. Recent Advances in Oral Cancer:

8.1 Chemotherapy: Chemotherapeutic agents or radioactive drugs are used in the treatment of oral and other cancers. Chemotherapy and immune therapy drugs play an important role in the treatment of oral cancer. Chemotherapy is used in the primary treatment of oral cancer and in combination with radiotherapy. Extension of survival is possible with only chemotherapy protocols. Survival rates of 30–60% at three to five years are now being reported. Patient selection for these intense treatment regimens must take careful consideration of the patient's overall clinical status [57]. Treatment by highly skilled physicians with multidisciplinary radiotherapy, medical, surgical, nursing and other supportive care is desired to tolerate these patients through such intense

treatment protocols [58]. Chemotherapy is considered especially for those patients who are ineligible for surgery. It is determined that associated targeted agents with radiotherapy combinations cause lower treatment-related toxicity, have low operating curability rates, or harbour tumours for which non-surgical therapy represents a more acceptable treatment. While adjuvant chemotherapy has not been significant used in the treatment of oral cancer patients after surgery. There is no evidence of the benefit of chemotherapy in the treatment of head and neck cancer.

8.2 New Approach in Chemotherapy: New chemotherapeutic drugs have been developed that may be more effective for the treatment of oral cancer. Intra-arterial chemotherapy has been examined in combination with radiation therapy for improving its effectiveness, in which drugs are injected directly into the bloodstream. Another new approach is introduced intra-lesional chemotherapy for head and neck cancers treatment, in which chemotherapy drugs are injected directly into the tumor. But, it has side effects that these drugs are tended to the nearby tissues and rest of the body. Therefore, its use is limited for treatment. To reduce the side effects of chemotherapy drugs, researches made a drug solution so that it can be made localized treatment.

8.3 Chemoradiotherapy: Chemoradiotherapy is the study of chemotherapy with the combination of radiation. In this process, chemotherapy acted as a radiation sensitizer and is used to reduce radiation resistance. Studies suggested that chemoradio-therapy is a better approach than radiotherapy alone in cancer patients, but it has a great risk of reappearance of cancer. In the European Organization for Research and Treatment of Cancer (EORTC), 334 patients were tested with either cisplatin 100mg/m^2 with radiation and radiation alone at same time interval (day 1, day 22, and day 43) [59, 60]. The same experiments were carried in Radiation Therapy Oncology Group (RTOG), which treated 459 patients [61, 62]. Unfortunately, they came to different conclusions about the advantage of chemoradiation. Based on investigation of these two studies, adjuvant chemoradiation gave better results than only radiation. Therefore, chemo-radiotherapy can be applied on oral cancer patients. Radiotherapy is a local treatment in oral cancer and local control plays an important role in getting cure from cancer suppression [63, 64, 65]. While metho-trexate (anti-metabolites) is commonly used for palliative chemotherapy, platinum chemotherapy is also most active drug compound for the treatment of head and neck cancer, however the survival time rate of cancer patients, is exceeded rarely six months [66]. According to Leon [67], survival time is fallen to approximately three months in patients who had treated failed platinum-based therapies.

However, radiation has side effects. Chemotherapy is a systemic treatment that goes *via* bloodstream throughout the body and chemoradiotherapy is a localized treatment that is worked at a specific site. Therefore, radiation side effects have been seen in cancer patients at the part of body where radiation therapy is being given. While most cancer patients do not feel side effects like nausea or vomiting if stomach is not the part of the treatment (there are many medicines that are used to minimize the side effects of the radiation) and similarly hair loss is seen in the cancer patient which has been gone to treatment of head. Because of radiation therapy is area specific treatment; therefore, side effects also see at the area which has been undergone the treatment. For example, if male patients undergo radiotherapy in oral cancer, then he will loss teeth and bread hair permanently.

While some cancer patients feel fatigued during radiation therapy. Skin irritation and mucositis are most common side effects and get worse with time as treatment carries on. However, after treatment, the body starts to repair this harm, salivary begin functional.

8.4 Other Approaches:

8.4.1 DNA Changes in Oral Cancer: It is still an unknown factor what DNA modifications are responsible for causing cells of the oral cavity and oropharynx to become cancerous. Mutation in the p53 gene of the oral cavity is responsible for oral cancer. The protein product of the p53 gene commonly works to prevent cells from growing too much and helps to destroy cells with DNA damage too extensive for the cells to repair. The p53 DNA damage can lead to the overgrowth of abnormal cells and the formation of cancers. Multiple studies suggest that detection of the p53 gene can allow detecting cancer at a very early stage that can be

treated at a time. These tests also provide margin to the doctors for checking that all cancer cells can be removed or not. Another DNA change was found in oral cancers, in which DNA of human papillomavirus (HPV) mixes together with the patient's own DNA.

8.4.2 Gene Therapy: Gene therapy is being used in cancer studies. In gene therapy, it is determined that how can be reversed DNA changes in oral cancer. Therefore, the results of the DNA changes can be stopped to become cancerous.

8.4.3 Tumour Growth Factors: Studies suggested that growth factors (hormone-like substances) promote cell growth in the body. The growth factor attaches to growth factor receptors to activate the cell for unlimited growth. One of the growth factors that have been linked to oral and oropharyngeal cancers is called epidermal growth factor (EGF). Oral and oropharyngeal cancers with too many EGF receptors tend to be especially aggressive [68.]

8.4.4 Vaccines: Most people think of vaccines as a way to prevent infectious diseases such as polio or measles. However, vaccines are being studied as a way to treat people with cancer by helping their immune to recognize and attack the cancer cells. Since some oral and oropharyngeal cancers contain DNA from human papillomaviruses, vaccines against these viruses are being studied as a treatment for these cancers. Biological treatment alone and with radiotherapy can be a good approach for treatment than the other approaches. Researchers need to focus on targeted agents, such as the EGFR inhibitors and the VEGF inhibitor bevacizumab, which have added a new dimension to potential treatment [69].

CONCLUSION: Oral cancer is deadly cancer as it has the first rank in the Indian subcontinent. But still, there is no proper treatment and early-stage diagnosis. The most appropriate treatment is chemoradiotherapy. Intra-arterial and intra-letional chemoradiotherapy are new approaches for the treatment of oral cancer. Government should run an awareness program to the citizens. As many surveys suggested that people are no aware of the reason for oral cancer, and it can be preventable or not. They even do not know that it could be genetic. If oral cancer detects at an early stage, then it could be treated successfully. Therefore, it becomes a necessity to develop the method for early detection of oral cancer. As we also know oral cancer can be examined by self. So that it is compulsory that every person should to examine oral cancer once in a month.

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