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Burden of diabetes and oral cancer in India

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ABSTRACT

Oral cancer and diabetes are highly prevalent among the Indian population and are part of the top four non-communicable diseases responsible for mortality and morbidity. Their numbers are so great that they pose a unique burden to the socioeconomic growth of the country. In recent years, there has been an increase in the number of studies examining the role of diabetes in oral cancer reporting co-existence of diabetes and cancer. There is also growing evidence of a higher risk for developing a number of cancers among individuals with diabetes, including pancreatic, liver, gynecologic, colorectal, oral and breast cancer, and consequently 'diabetic oncopathy' is emerging as one of the complications of diabetes. Diabetes may lead to the development of cancer through oxidative damage leading to accumulation of DNA mutations and/or through immune dysfunction, which predisposes to viral infection. Cancer and diabetes may co-occur due to shared risk factors such as increased insulin-like growth factor-1 and obesity, but there is no clear biologic link between the two disorders. This literature review aims to review the evidence showing the current burden of two non-communicable diseases, diabetes and oral cancer and their potential association, with particular reference to India.

Contents

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1. Introduction

Major health transitions occurred over the second half of the 20th century (known as an epidemiological transition) due to changes in socioeconomic and technological conditions. There was a rapid increase in human capacity to use science to prolong and enhance life, however, a consequence of these health transitions has been a globally pervasive rise in the burden of non-communicable diseases (NCD).[1] Globally, according to the World Health Organization (WHO) the four NCDs which make the greatest contribution to morbidity and mortality, and are responsible for 82% of all NCD deaths, are cardiovascular diseases, chronic respiratory disease, cancers and diabetes.[2] In 2016, cancer and diabetes were responsible for 9.0 million and 1.6 million of all NCD deaths respectively.[3] Globally, the burden of cancer and diabetes are expected to increase in the next decades, particularly in developing countries such as India, with cancer predicted to become the leading cause of death in the 21st century and the main obstacle to increasing life expectancy.[4] Available evidence suggests that certain forms of cancers, including cancer in the oral cavity, are more frequently observed in individuals with diabetes.[5]

In India, NCDs account for an estimated 62% of the total disability adjusted life-years lost and result in over 5 million annual deaths, accounting for nearly three out of every five deaths across the country.[6] The burden of cancer and diabetes is significant in developed and developing economies, such as India, and these two NCD's share risk and contextual factors.[7] Globally India ranks second with regard to the number of individuals living with diabetes.[8] Various cancer types, including colorectal, liver, pancreatic, endometrial, breast and ovarian cancer, have been linked to Type 2 Diabetes Mellitus (T2DM).[9] Various studies have assessed the association between both oral cancer and diabetes, however, the results are equivocal.[10,11]

Available data show that both diabetes and oral cancer are rapidly becoming public health issues in developing countries such as India but the magnitude of the problem associated with their coexistence is not known.[4,9] The aim of this review is to determine the burden of oral cancer among individuals with diabetes, the predisposing factors connecting both diabetes and oral cancer and possible biological mechanisms for the synergies, especially in India.

2. Data source

The literature search was performed using two different data sources. Firstly, an electronic search was performed for articles describing the relationship between oral cancer and diabetes including incidence, prevalence, risk factors and mechanisms of diabetes and oral cancer using PubMed from inception to March 2020. The key search terms comprised 'diabetes' or 'oral cancer' or 'prevalence of diabetes' or 'incidence of diabetes' or 'prevalence of cancer' or 'incidence of cancer' or 'link/association/relation between diabetes and oral cancer' or 'risk factors for diabetes' or 'risk factors for oral cancer' or 'biomarkers for diabetes' or 'biomarkers for oral cancer' with 'India' and 'worldwide'. Secondly, a search for appropriate studies was performed by reviewing references in articles and local journals related to cancer and diabetes in Embase, CINHL, Web of Science, Public health Database, IndMED, Google or Google scholar and grey literature reports. The search was restricted to publications in English with no set date or study restrictions and a combination of free text and MeSH terms was applied. The inclusion criteria for article selection was original studies and review articles where the minimum age of participants was 18 years and above. Articles were excluded if data were collected from individuals without diabetes and/or cancer.

3. Burden of diabetes mellitus

Diabetes is considered by WHO as an apparent epidemic which is strongly related to lifestyle and economic change.[12] Diabetes is emerging as a global pandemic and T2DM makes up 90–95% of all diabetes cases around the world. The prevalence of T2DM has gradually increased in recent years and is predicted to increase dramatically over the next decades.[9] The prevalence of diabetes has increased more rapidly in low-income and middle-income economies compared to high-income economies. Globally, diabetes is an important cause of premature mortality and morbidity as it has many complications that can escalate the overall risk of mortality. Hyperglycemia, commonly seen in uncontrolled diabetes, may lead to serious damage to the eyes (retinopathy), heart, kidneys (nephropathy), blood vessels and nerves (neuropathy).

3.1. Epidemiology of diabetes-the global scenario

According to the International Diabetes Federation (IDF), worldwide the number of individuals with diabetes has risen from 194 million in 2003 to 463 million in 2019 and is predicted to reach 578 and 700 million by 2030 and 2045 respectively.[13] In 2019, the global prevalence of diabetes was 9.3%.[9]

According to IDF, in 2019, eight of the top 10 countries with the highest number of individuals with diabetes are developing nations.[9] Globally, China has the largest number of people with diabetes (116.4 million) followed by India (77.0 million). It is estimated that by 2045 China will have 147.2 million people with diabetes followed by India with 134.2 million (Table 1).[9] The escalation in the number of individuals with diabetes is primarily attributable to the increased population in these countries. In the developing nations, the rate of increase in

Table 1
Top ten countries for number of individuals with diabetes among those aged 20–79 years (2019 and 2045) (International Diabetes Federation, 2019) [Ref no:9].

Country	Individuals with diabetes in 2019 (millions)	Rank based on numbers in 2019	Estimated individuals with diabetes in 2045 (Millions)	Rank based on estimated numbers in 2045
China	116.4	1	147.2	1
India	77.0	2	134.2	2
United States of America	31.0	3	36.0	4
Pakistan	19.4	4	37.1	3
Brazil	16.8	5	26.0	5
Mexico	12.8	6	22.3	6
Indonesia	10.7	7	16.6	8
Germany	9.5	8	–	–
Egypt	8.9	9	16.9	7
Bangladesh	8.4	10	15.0	9
Turkey	–	–	10.4	10

diabetes is mostly due to the rapid transition in the epidemiology and nutritional factors. The increase in people with diabetes is mainly due to ageing and population growth in the largest countries in the world. In addition, other contributing factors include physical inactivity and unhealthy diet.[14]

3.2. Epidemiology of diabetes-the Indian scenario

Currently, India is experiencing a change in the prevalence of diabetes from the wealthy to the less privileged; urban to rural areas; and older to younger individuals.[15] Recent studies in India have shown that in both urban and rural areas the problem of diabetes has increased rapidly.[15] In India, the burden of T2DM increased steadily in the 1990s and rapidly from the year 2000 onwards. The proportion with diabetes, according to epidemiological studies conducted in India, has risen from 5.8% in the year 2000 to 10.4% in 2019.[9,16] Few nationwide studies have been conducted to assess the prevalence of diabetes. The prevalence of diabetes was reported to be 2.1% in the multicenter survey conducted between 1972- and 1975 in Ahmadabad, Cuttack, Calcutta, Delhi, Trivandrum and Pune and in the adjacent rural areas.[17] The recent ongoing nationally representative epidemiological survey, called the ICMR–India DIABetes (INDIAB) study, estimated the prevalence of diabetes in India to be 7.3%.[15,18] On comparing two Asian Indian populations, one residing in San Francisco and Chicago, USA and the other in Chennai, South India, Gujral and colleagues reported that the prevalence of T2DM was 38% in Asian Indians residing in Chennai, which was slightly higher when compared to 34% among those residing in San Francisco.[19] These results suggest that the current epidemiological and demographic transitions occurring in India are similar, if not worse, than in the USA, thus increasing the risk for T2DM.

The increase in T2DM prevalence could be attributed to the rapid lifestyle changes that have occurred over the past five decades, including unhealthy eating habits (increased intake of refined cereals, fat, salt and sugar) and low levels of physical activity.[20] An increase in diabetes risk has also been associated with various exposures such as smoking, depression, the built environment, environmental pollutants and short sleep duration.[14]

4. Burden of oral cancer

The term 'cancer' is used to classify or compartmentalize a large group of disorders distinguished by uncontrolled, abnormal growth of cells that attack and spread to adjacent spaces or organs.[21] Oral cancer, which is defined as cancer of the lips, mouth and tongue, is one of the most common cancers to occur in the Indian population and this is largely attributed to the use of tobacco (chewing/smoking forms).[22] The most common site of oral cancer is the buccal mucosa followed by the alveolus and tongue. Oral squamous cell carcinoma (OSCC) is the most common type of cancer reported in the oral cavity and represents 80–90% of all malignant tumors.[23] Leukoplakia, a condition where thick, white or grayish patches form, is a premalignant lesion which has been linked to OSCC. Leukoplakia occurs in all places within the oral cavity with a high frequency reported in the buccal and mandibular mucosa regions.[24] OSCC is characterized by poor diagnosis and high mortality rates, with a 5-year survival rate of about 65%, despite improved imaging techniques and advances in radiotherapy, chemotherapy and surgery.[25,26] The best prognosis and 5-year survival rate is seen for cancers on the lip region and in younger patients.[24]

4.1. Epidemiology of oral cancer - the global scenario

Oral cancer was the sixth most frequently occurring cancer globally in 2012, accounting for between 2 and 4% of all cancers.[27] The yearly incidence of oral cancer was more than 300,000 cases, of which 62% occurred in developing countries.[28] According to the 2018 WHO Global cancer statistics, oral cancer incidence is ranked seventeenth worldwide with a yearly incidence of 354,864 cases (cumulative risk: 0.46). The worldwide incidence of oral cancer is 2%, with a mortality rate of 50% among them. However, in the South East Asian region (SEARO), oral cancer is ranked fourth (incidence rate - 7.4%) and in India it accounts for 10.4% of all malignant cancers and ranks second among all cancers (Fig. 1).[4]

Oral cancer is much more common in developing countries, such as India, than in developed countries, however in recent years there has been an increasing trend due to changes in people's lifestyle. Oral cancer is the most common type of cancer in South Asian Countries such as Bangladesh, India, Pakistan and Sri Lanka, and these areas account for almost 25% of all new cases of oral cancer.[29] There is a marked geographical variation in the incidence and prevalence rates of oral cancer in this region. The highest incidence rates of oral cancer are in the South and Southeast Asian regions. Similarly, a high incidence of oral cancer has been reported in regions of the Caribbean (Brazil and Puerto Rico), Pacific (Melanesia and Papua New Guinea) and Western Europe (Slovakia and Slovenia).[29]

Among men, a high incidence of oral and oropharyngeal cancers has been reported in European countries.[30,31] Information collected from 13 French population-based registries in 2010 on 1089 oral tumors highlighted that 75% of the cases were males, with tonsil and tongue being the major sites of cancer.[30] In Northeastern Hungary, OSCC occurred most frequently in the floor of the oral cavity (27.7%), followed by lip (26.9%) and tongue (22.7%), with a five-year survival rate of 38.7%.[31] In Australia and New Zealand, the incidence rates/100,000 were 9.4 and 3.7 in men and women respectively in 2018 and in North America the incidence rates were 6.3 and 2.4. In Papua New Guinea, where betel nut chewing, tobacco use, and heavy alcohol consumption are common, lip and oral cavity were the most frequent sites of cancers.[4]

4.2. Epidemiology of oral cancer-the Indian scenario

In the Indian subcontinent, oral cancer is a major public health issue accounting for 10.4% of all cancers. Incidence has escalated over the past two decades and, according to the GLOBOCAN 2018 report, oral cancer is the second most frequently occurring cancer in India, with a mortality rate of 9.3% (Fig. 2).[4] Among males, the most frequent type of cancer is oral cancer followed by lung cancer.[4] Geographically, the central region of India has the highest incidence of oral cancer, with the highest rates in those aged over fifty. Recently, however, there has been a rising trend in incidence rates of oral cancer among younger patients in

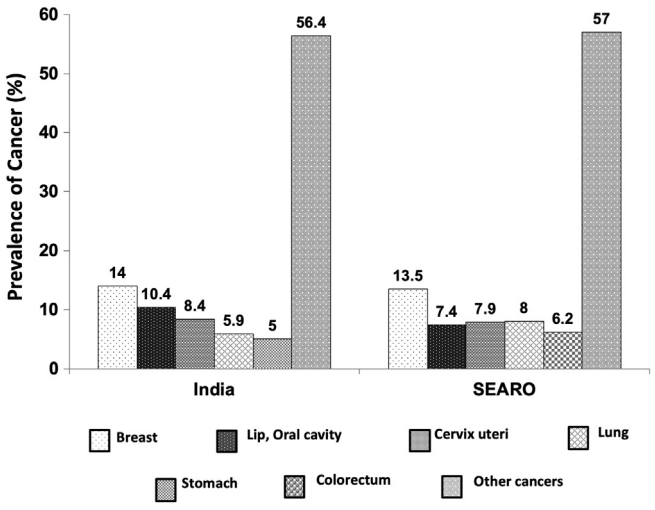

Fig. 1. Percentage of new cancer cases in South East Asian region in 2018 [Ref No: 4].

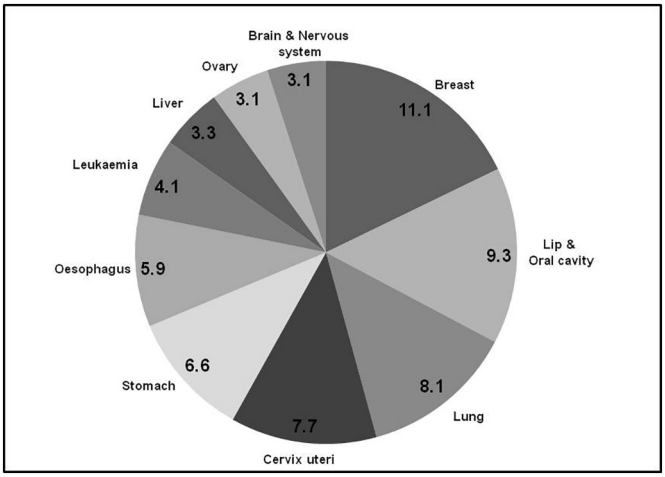

Fig. 2. Mortality rank of top ten cancer sites in India according to GLOBOCAN 2018 [Ref No: 4].

India and around the world.[32] Among the populations of Europe and the United States, the most common sites of oral cancer are the tongue, while in the Southeast Asian and Indian regions it is in the buccal mucosa. The widespread use of moist snuff held between the buccal mucosa and gingival region and the increased risk of oral cancer associated with this practice, explains why buccal mucosa is a common site in India and Southeast Asia.

An Indian study conducted in Allahabad reported tongue as the most common site of oral lesions and increased incidence rates of tongue cancer.[33] In another study (rural western Maharashtra), buccal mucosa was reported to be the most common site of oral cancer.[34] A review, which provided an update on the epidemiology of oral cancers between 2000 and 2012, reported that in India the most common sites of oral cancer were the tongue, the buccal mucosa and gingival.[35]

In India, population-based cancer registries have reported age adjusted rates for oral cancer to be higher in young males. This trend was observed in the western and northern regions of the country.[32] The Population-Based Cancer Registry data (1990–2014) in Delhi reported oral cancer incidence trends over a 24-year period. The results showed an increasing trend since the year 2003 in the proportion of oral cancer among all types of cancer in Delhi.[36] Similar trends have been reported in the National Cancer Registry Program data from Mumbai, which reported an increasing trend in incidence rate (3.3% each year) of oral cancer in men over a decade (1999–2009) and a moderate increase among women over 7 years (2002–2009).[37] These differences and variation in the trend in the subcontinent could be due to regional differences in the occurrence of certain risk factors and the ageing of the population.

5. Is diabetes, a determinant for oral cancer or vice versa?

Various studies have reported a strong relationship between T2DM and cancer and have reported co-occurrence of diabetes and cancer.[38–40] Cancer and diabetes may co-occur due to shared risk factors, but there is no clear biologic link between the two disorders.

5.1. Biological mechanisms linking T2DM and oral cancers

5.1.1. Hyperinsulinemia

T2DM is usually related to an increased secretion of insulin resulting in hyperinsulinemia.[14] Hyperinsulinemia has been shown to be associated with breast, pancreas and colon cancers. This role of cancer promotion by insulin was first recognized in experimental animal studies.[41] It has been reported that insulin receptors are expressed by cancer cells.[42] An observational study concluded that non-obese individuals with hyperinsulinemia were at increased risk of mortality related to cancer than those without hyperinsulinemia.[43]

Two postulated pathways for action of insulin in cancer proliferation:

1. Insulin/Insulin Like Growth factor-1 (IGF-1) axis-

Growth hormones play a major role in growth and development of tissue and several studies have considered the relationship between circulating levels of IGF-1 and cancer. A few studies have shown a modest correlation with higher circulating levels of IGF-1 and cancer, while others have shown no association at all. Insulin and IGF-1 have a major role in the activation of cell proliferation, differentiation and survival.[44]

Hyperinsulinemia increases IGF in the body. Increased insulin levels decrease the production of Insulin Like Growth Factors Binding Protein-1 (IGFBP-1) and Insulin Like Growth Factors Binding Protein-2 (IGFBP-2) in the liver leading to an increase in the presence of free circulating IGF-1. IGF-1 and IGFBP-3 are mainly involved in normal cell growth by promoting cellular proliferation and having an anti-apoptotic role. The circulating IGF-1 binds to the IGF-1receptor (IGF-1R), a tyrosinase kinase receptor which resembles the insulin receptor (IR), which in turn triggers a signaling cascade through the AKT pathway, which then acts on the target genes and promotes cell proliferation, survival, invasion and angiogenesis.[45,46] The activation of the IGF-1R also down regulates the cell cycle suppressors. In carcinogenesis, they regulate proliferation and inhibit apoptosis, control metastases and clonal expansion of cells.[47]

The majority of cancer cells express insulin receptors, IGF-1 receptors (IGF-1R) and hybrid receptors. The IGF-1 and hybrid receptors are involved in cell growth and proliferation while the insulin receptor is involved in the metabolic functions. Serum analysis of IGF-1 and IGFBP-3 in oral cancer patients has shown that there is a decrease in the levels of IGF-1 and IGFBP-3 when compared to controls.[48] Shpitzer et al. estimated the salivary levels of IGF-1 and reported that IGF-1 concentrations were 117% higher in oral cancer patients ($p = 0.03$).[49] Low serum IGF-1 levels are associated with T2DM.[50] Zhi et al. investigated the levels of IGF1, IGF 2 and IGFBP-3 in human cancer tissue and normal epithelium tissue and reported that there is no alteration in the tissue levels of IGF 1 and IGF2.[51] However, they found an up regulation of IGFBP-3 in cancers when compared to normal tissues.

2. Unregulated signaling of the insulin receptor

It has been hypothesized that hyperinsulinemia promotes carcinogenesis by stimulating the proliferating pathways distal to the insulin receptors. Insulin has an anti-apoptotic role probably through the phosphatidylinositol 3 kinase and extracellular signal regulated protein kinase pathways in HepG2 cells.[52]

5.1.2. Hyperglycemia

Hyperglycemia is also a known promoter of carcinogenesis and metastasis.[53] All cancer cells require glucose for energy. Hyperglycemia can lead to excessive free radical formation which promotes carcinogenesis. A clinical study found that diabetes is associated with increased production of reactive oxygen species (ROS) and increased oxidative damage to DNA, which in turn leads to unfavorable mutations in the oncogenes and tumor suppressor genes, contributing to cancer development.[54] In their clinical study, Sen et al. concluded that the risk of oral cancer increased two-fold in individuals with hyperglycemia.[55]

5.1.3. Chronic inflammation

There has been an increasing level of evidence suggesting the role of inflammatory mediators in the role of carcinogenesis and diabetes mellitus. Poorly controlled diabetes mellitus may lead to the development of a permanent pro-inflammatory condition. Inflammatory cytokines like interleukin-6, interleukin 1 beta, interleukin-8, and positive acute phase proteins like C-reactive proteins have been proven to play a role in

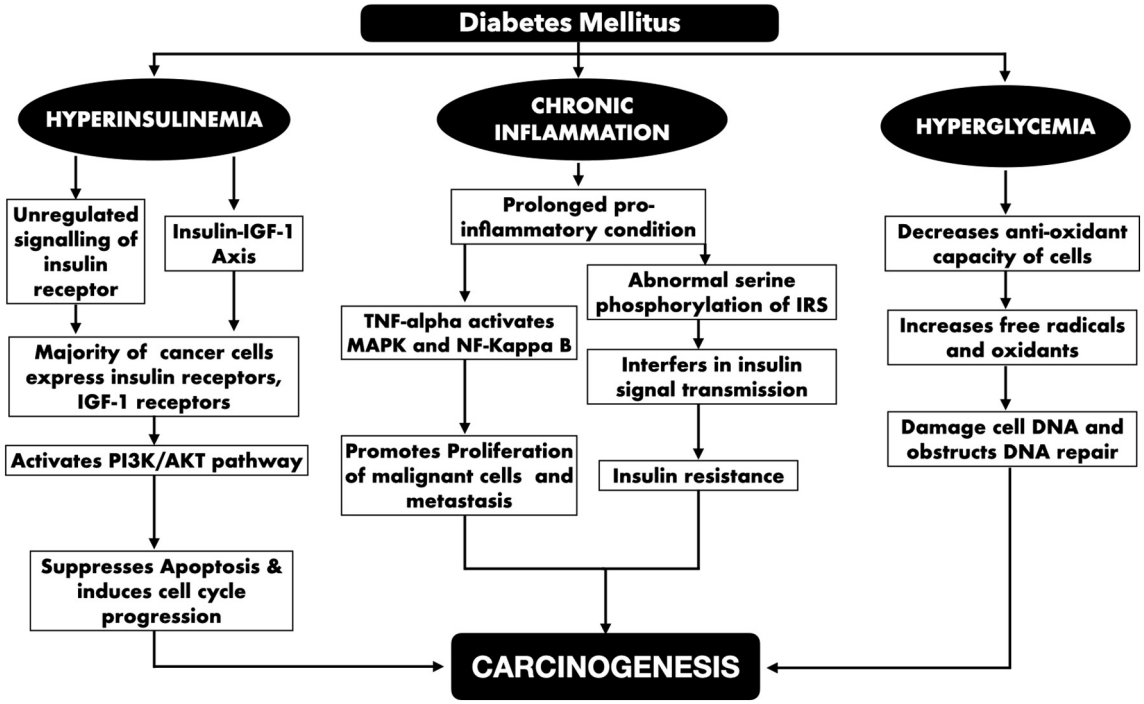

Fig. 3. Biological mechanisms linking T2DM and oral cancers.

carcinogenesis.[56] Interleukin-6 and C-reactive proteins have also been linked to the development of T2DM. TNF-alpha activates MAPK and NF-κB and promotes proliferation of malignant cells and metastasis.[57] These inflammatory markers can be identified in the saliva of patients. Various studies have shown the presence of elevated TNF-alpha, IL-6, IL-1beta, IL-8 and C-reactive proteins in the saliva of patients with oral cancer.[58,59] High levels of C-reactive protein have also been implicated in the prognosis of patients with oral cancer. Fig. 3 summarizes the potential biological mechanisms linking T2DM and oral cancers.

6. Common risk factors for diabetes and oral cancer

Several developing countries have experienced rapid transitions in economics, lifestyle and nutrition and these have contributed to the increase of NCDs including diabetes and cancer. Shared risk factors build the case for an association between cancer and diabetes. Non-modifiable risk factors for both conditions include ageing, ethnicity, gender and genetic makeup, while modifiable risk factors include physical inactivity, excess alcohol consumption, an unhealthy diet and tobacco use (Fig. 4). Improved knowledge of these determinants is important to inform our understanding of the etiology of any associated diseases.

6.1. Age and gender

The prevalence of both diabetes and cancer are known to increase with increasing age. Historically, diabetes occurred predominantly in people above 65 years of age in developed economies. However, in

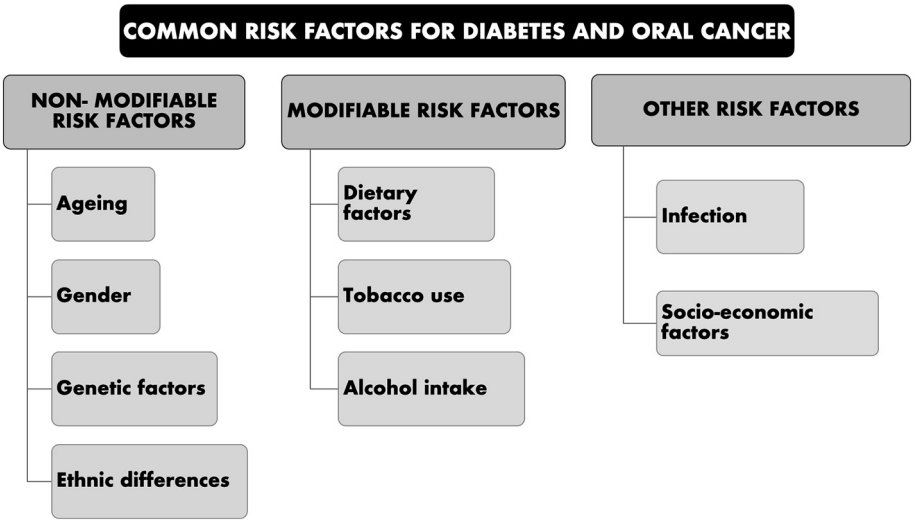

Fig. 4. Shared risk factors for diabetes and oral cancer.

India, studies have reported that the onset of diabetes commonly occurs in a younger age group (25–34 years).[15,18] Oral cancer usually develops in people above 50 years of age, peaking in those in the 60–70 year age group.[29] Overall, the global prevalence of diabetes is higher in men than women and in the ICMR-INDIAB study the prevalence of diabetes in men aged 35–65 years was significantly higher than for women in the same age range.[18] Similarly, oral cancer is more prevalent in males than their female counterparts with a ratio of 1.5:1.[29]

6.2. Genetic factors

Both T2DM and oral cancer have a strong familial component. T2DM is a polygenic disorder with many susceptibility genes.[14,60] A few genetic abnormalities are also known to increase the susceptibility to cancer. Individuals with Li-Fraumeni syndrome (mutation of p-53 tumor suppressor gene), Fanconi's anemia and Bloom syndrome have also been reported to have an increased susceptibility to cancer.[61,62]

6.3. Ethnic differences

Studies have shown that individuals of specific ethnicities are more prone to develop T2DM and oral cancer. In the USA, for instance, Hispanics (14%) and African Americans (12%) have higher rates of diabetes relative to non-Hispanic whites (7%).[63] The risk of oral cancer is higher among Indians in Malaysia compared to the Chinese and, non-migrant Australians have higher rates of mouth cancer compared to migrants from the Mediterranean littoral and the Middle East.[64,65]

6.4. Dietary factors

Dietary factors also play an important role in both T2DM and cancer prevention. Traditional diets, i.e. high consumption of vegetables, fruits, whole grains and legumes are slowly disappearing due to a rapid nutrition transition in India.[14] Urbanization and modernization have changed the dietary pattern of Indians to consumption of high caloric foods and foods high in fat. There has been an increase in the intake of meat, animal products, sugar, sweetened beverages, and processed foods coupled with low consumption of vegetables, fruits and fiber. Increased consumption of fruits and vegetables, low fat products and whole grains has been associated with lower risk of developing T2DM.[66–68] Similarly, high consumption of fruits and vegetables has been shown to reduce the risk of oral cancer due to the presence of carotenes, vitamin C, anti-oxidants and fiber in the fruits and vegetables.[69]

6.5. Tobacco use

There is emerging epidemiological evidence to show that there is strong association between cigarette smoking and development of T2DM and oral cancer. Population based studies have shown associations between cigarette smoking and the development of T2DM.[17,70] The Health Professionals' Follow-Up Study conducted among 40,000 American male health care professionals reported that smoking ≥25 cigarettes/day had a relative risk of incident diabetes of 1.94 compared to those who did not smoke.[71]

The most common cause of oral cancer (90%) is the use of tobacco either in smoked form or by chewing. Tobacco contains over 60 known carcinogens.[72] The smoking forms of tobacco are cigarettes, cigars, pipe, bidis etc. The chewing forms of tobacco are called moist snuff, khaini, pan varieties etc. Cigarette smoking is the most common cause of oral cancer. In India, according to the report of the Global Adult Tobacco Survey (2016–17), 28.6% of adults use tobacco.[72] Betel quid (areca nuts and staked lime wrapped in a betel leaf) contains tobacco and chewing this mixture is a popular pastime in India. A systematic review of studies from South Asia looking at the association between oral cancer and smokeless tobacco reported that the increased relative risk for oral cancer with use of betel quid varied from 3.1 to 15.7 and for chewable tobacco it varied from 1.2 to 12.9.[73] Similarly pan or betel quid chewing leads to development of a precancerous condition called oral submucous fibrosis, which may later turn into cancer. In Trivandrum (India), a randomized control study reported tobacco chewing as the strongest determinant associated with oral cancer.[74]

6.6. Alcohol consumption

Alcohol is considered carcinogenic to humans and has been associated with cancers of the liver, oral cavity, oesophagus, pharynx and larynx. Alcohol intake has a synergistic effect with tobacco in the causation of oral cancer. Alcohol acts as a solvent, increasing the membrane permeability of the carcinogens into the mucosa. A case-control study conducted in southern India (Bangalore, Madras and Trivandrum) included 591 incident cases of oral cancer and reported an odds ratio of 2.2 for alcohol consumption and that among men, 35% of oral cancers were due to smoking and alcohol consumption.[75] In south India, a case-control study reported that bidi smoking and alcohol consumption emerged as significant risk factors for oral cancer.[76] Alongside established lifestyle factors, alcohol consumption also plays an important role in the development of T2DM. A meta-analysis conducted in T2DM using data from 20 observational studies, found peak risk reduction at 24 g/day (relative risk: 0.60) among women and 22 g/day (relative risk: 0.87) among men, compared to those who did not consume alcohol, indicating that the risk for diabetes is increased above these levels of alcohol consumption.[77] In a case control study conducted in south India, a positive association between alcohol and diabetes has been reported.[78]

6.7. Other risk factors

Certain viral infections including hepatitis virus, Epstein–Barr virus (EBV), and human papilloma virus (HPV) may also be involved in oral cancer.[79,80] A recent study described T2DM as one of the patient specific factors for HPV-16 positive head and neck carcinomas.[79] Those who were HPV-16 positive also showed an improved disease specific survival. Schildt et al. reported a strong association of HSV-I with oral cancer and another study found a significant difference in the HSV-I IgG levels among those with and without oral cancer.[80,81] Sun and coworkers reported a higher prevalence of HSV-1 infection in individuals with diabetes compared to those without diabetes and have shown a significant association of HSV-1 infection with T2DM.[82]

Socioeconomic factors can also be evaluated as risk factors for the development of T2DM and oral cancer. Recent research shows that lower economic status measured by occupation, education or income are also risk factors for both oral cancer and diabetes.[18,83]

7. Available evidence linking diabetes and oral cancer

To date, studies that have evaluated the relationship between diabetes and oral cancer have produced equivocal results (Table 2).[5,10,11,39,40,84–92] Wideroff and colleagues conducted a population based retrospective study of all cancers by linking computerized records from the Danish Central Hospital Discharge Register ($n = 109{,}581$) and cross-checking them with the cancer registry in Denmark.[11] They reported that patients aged <50 years have a 2–3 fold increased risk of developing oral cancer compared with those >50 years of age. A marginal excess of cancers of the mouth and pharynx (Standard incidence ratio:1.5) was also observed in patients with T2DM.

Ujpál and colleagues investigated the relationship between diabetes and oral tumors in Hungary. The researchers conducted a retrospective case-control study and a cross-sectional stomato-oncological screening study of patients. This study reported higher prevalence of benign tumors (14.5% vs. 6.4%) and precancerous lesions (8.0% vs. 3.2%) among individuals with diabetes compared to controls respectively.[39]

Table 2
Studies that included data on the relationship between diabetes and oral cancer.

Author, year, place [Ref]	Study design	Site of cancer	Sample size (n)	Risk estimates for oral cancer	Findings related to oral cancer
Positive results					
Wideroff et al., 1997, Denmark [11]	Retrospective Population based cohort study	All sites	1,09,581 individuals with diabetes	–	Chance for an elevated risk of oral cancers were observed in cohort members prior to the age of 50 years
Ujpál et al., 2004, Hungary [39]	Retrospective Case-control study	Oral	Cases with oral cancer-610; Controls-574	–	14.6% of the oral cancer patients had diabetes-significantly higher than cancer-free group
Kuriki et al., 2007, Japan [84]	Case-control study	All sites	Cases with cancer-11,672; Controls-47,768	Odds Ratio- 2.0 (0.9–4.8)	Patients with diabetes have a 40% increased risk for cancers in all sites compared to those without diabetes
Bosetti et al., 2012, Italy and Switzerland [40]	Case Control Study	All sites	Cases with cancer-12,689 (1468 oral and pharyngeal); Controls-12,060	Odds Ratio- 1.6 (1.2–2.2)	Risk of developing oral cancers persisted over 10 years since diagnosis of diabetes. Diabetes may increase the risk of oral cancer
Tseng et al., 2014,Taiwan [85]	Retrospective cohort case-control study	Head and Neck	Cases-89,089 Control-89,089	Hazard Ratio- 1.7 (1.5–2.1)	The risks of developing oral cancer was significantly higher in patients with diabetes
Gong et al., 2015 [5]	Meta-analysis	Oral Cancer	–	Summary Relative risk-1.15 (1.02–1.29)	Type 2 diabetes was associated with increased oral cancer incidence and mortality
Lin C.M et al., 2015, Taiwan [86]	Retrospective population based cohort study	All sites	Cases-36,270 Controls-145,080	Hazard Ration- 1.13 (0.95–1.34)	Patients with diabetes had a higher risk of oral cancer after adjusting for confounding factors
Vegh et al., 2017, Hungary [87]	Retrospective Case-control study	Oral	Cases with oral cancer-758; Controls-534	–	Diabetes was found present in 25.9% and IFG in 20.6% of patients with oral cancer
Cheng et al., 2020, Taiwan [88]	Retrospective hospital based cancer registry	Oral	Cases with oral cancer-191	Hazard ratio -1.87	Oral cancer patients with diabetes, presented lower 5-year overall survival rates
Ramos-Garcia. et al., 2020 [89]	Meta-analysis	Oral cancer	–	Odds Ratio-1.41 (1.1.-1.81) Hazard Ratio-2.09 (1.36–3.22)	Patients with T2DM had an increased risk of oral cancer and also an increased mortality to oral cancer.
Negative results					
La Vecchia et al., 1994, Italy [10]	Case-control study	All sites	Cases with cancer-9991 Controls-7834	Relative Risk- 0.5 (0.2–1.1)	Diabetes is not a risk factor of oral cancers
Tseng CH, 2013, Taiwan [90]	Retrospective population based cancer registry	Oral	9,98,540 healthy population	Relative Risk- Men-1.2 (0.9–1.6); Women-1.2 (0.8–1.9)	Diabetes is not a risk factor for oral cancer
Lai et al., 2013, USA [91]	Prospective cohort study	All sites	Individuals with oral cancer-1353	Hazard ratio -0.90 (0.73–1.10)	Diabetes was not associated with oral cancer
Li S et al., 2015, China [92]	Case-control study	Oral, oropharynx, larynx	Cases-921 Controls-806	Odds Ratio- 0.84 (0.39,1.80)	Diabetes was not associated with oral cancer after adjusting for confounders

In the Asian region, Kuriki and coworkers conducted a case-control study in Japan to assess the association between diabetes and multisite cancer risk among 11,672 incident cancer cases and 47,768 cancer-free controls.[84] The study reported that individuals with diabetes had twice the risk of developing oral cancer even after adjusting for age and other confounding factors.

Another review by Bosetti et al. reported on the relationship between diabetes mellitus and the risk of various cancers in a series of case-control studies conducted in Italy and Switzerland between 1991 and 2009.[40] The findings showed that the risk of developing oral cancers persisted over a decade from the diagnosis of diabetes and that diabetes may pose a 1.58 times increased risk for oral cancer.[40]

In Taiwan, a retrospective cohort study was conducted using the National Health Insurance Program Database. This study compared 89,089 newly diagnosed diabetic patients with at least two medical visits for diabetes mellitus and compared them with controls without diabetes ($n = 89{,}089$). After adjusting for all confounding factors, the study concluded that the risk for oral cancer was very high in individuals with diabetes.[85]

A retrospective case control study was conducted using data from 2012 to 2015 collected in a Department of Oral and Maxillofacial Surgery in Budapest, Hungary. Data from 758 patients with oral cancer and 534 tumor-free control patients were examined for the prevalence of diabetes and IFG and the distribution of tumor location. The study findings were also compared to data obtained 14 years earlier that had been collected from 1998 to mid 2002. Prevalence of diabetes (25.9% vs.14.6%) and IFG (20.6% vs. 9.7%) was significantly increased among oral cancer patients in the later study compared to the study conducted 14 years earlier.[87] This study indicates that the prevalence of oral cancer in diabetes is increasing and this may be related to lifestyle changes.

A previous 10-year (2002–2011) retrospective study conducted using data from the Cancer Registry Database of Taipei Veterans General Hospital included 191 patients with OSCC. The findings reported that patients with diabetes, presented lower 5-year overall survival rates (HR-1.87).[88] Two extensive meta-analyses have been undertaken and both are in agreement that there is an association between oral cancer and T2DM. Gong et al. reported that their findings indicated an elevated risk of oral cancer development in patients with T2DM.[5] Ramos-Garcia et al. also reported a higher prevalence of oral cancer in individuals with diabetes and that their mortality rate was higher.[89]

While many studies showed that diabetes is a risk factor for oral cancer, some studies have refuted these findings. A study by La Vecchia and colleagues investigated the relationship between diabetes and cancer risk utilizing data from a series of case-control studies conducted in northern Italy between 1983 and 1992.[10] They concluded that individuals with diabetes did not show any elevated risk of oral cancers. Similarly, in 2013 Tseng et al. utilized data from the National Health Insurance database in Taiwan to investigate the relationship between diabetes and cancer and they also concluded that diabetes is not a risk factor for oral cancer.[90] Likewise, in the prospective cohort of the National Institute of Health American Association of Retired Persons Diet and Health Study, Lai et al. reported that diabetes was not a determinant for oral cancer.[92]

Very few studies have looked at the association between diabetes and oral cancer in India. In the Indian subcontinent, Dikshit et al., in a cluster randomized controlled cancer screening trial, reported a strong relationship between premalignant lesions and diabetes.[38] These results provide evidence that the increased incidence of premalignant lesions can lead to a malignancy in individuals with diabetes. Another hospital-based study conducted in Manipal concluded that patients with hyperglycemia showed a two-fold increase in the risk of developing oral cancer.[55] In a hospital-based study conducted in Mangalore, South Karnataka, a high incidence of oral cancer (25.5%) was observed among 400 tumor patients. However, the findings reported a lower overall incidence of cancer in people with diabetes.[93] A recent observational study of 8352 participants who underwent opportunistic screening in a health promotion clinic in northern India reported that high random blood sugar had a strong association with oral cancer (OR = 2.3) even after adjusting for age and gender.[94]

8. Conclusions

Oral cancer and diabetes are public health issues that result in significant burdens for the healthcare system in India. From the available evidence, it remains uncertain whether diabetes is a determinant for oral cancer or vice versa. Some studies have shown that there is a relationship between the two conditions, but the mechanisms involved are clearly complex and require further elucidation. In individuals with diabetes and oral cancer, there is a need for a focused approach towards preventive, diagnostic and therapeutic strategies using interdisciplinary approaches involving health care professionals, including diabetologists and dentists. Further research is recommended to obtain comprehensive data to inform the epidemiology of these conditions and establish the mechanisms involved to understand their potential association.

Author contributions

Abhinav Rajendra Prabhu: Methodology, Review of literature, Writing - original draft.

Joanne Williams: Conceptualization, Validation, Manuscript review & editing, Supervision.

Patricia Livingston: Methodology, Validation, Manuscript review and editing.

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Declaration of competing interest

None to declare.

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