

Canadian Oral Cancer Report 2024

A Report by the Oral Cancer Group, Network for Canadian Oral Health Research

Working Group:

B Nicolau¹, S Madathil¹, S Iyer¹, N Eslamiamirabadi¹, H Kapoor¹, C Laprise¹⁻³, S Wurzba^{1,4}, WA Al-Soneider¹, C Dong⁵, M-C Rousseau^{2,3,6}

Affiliations:

- 1. Faculty of Dental Medicine and Oral Health Sciences, McGill University, Montreal, QC, Canada
- 2. Centre de recherche du Centre hospitalier de l'Université de Montréal, Montreal, QC, Canada
- 3. École de santé publique, Département de médecine sociale et préventive, Université de Montréal, Montreal, QC, Canada
- 4. Faculty of Medicine, Department of Otolaryngology, Head and Neck Surgery, McGill University, Montreal, QC, Canada
- 5. Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada
- 6. Institut national de la recherche scientifique (INRS), Centre Armand-Frappier Santé Biotechnologie, Laval, QC, Canada

Preface:

Given the significant increase in oral cancer cases in Canada in recent years, the Oral Cancer Group of the Network for Canadian Oral Health Research (NCOHR) recognized the need for a resource to support health professionals and individuals seeking insights about oral cancer in Canada.

The first step in developing this document was to engage with diverse stakeholders, including health professionals, researchers, students, residents, and others working in the field of oral cancer. Through one-on-one consultations with these stakeholders, we confirmed our belief that a report on the status of oral cancer in Canada could serve as a scientific resource for healthcare professionals and an educational tool for patients. Stakeholders shared insights that shaped the report's focus, highlighting areas such as prevention, early detection, and disparities in access to oral cancer care.

Informed by these perspectives, the report provides an overview of the epidemiological landscape of oral cancer, including incidence and mortality rates, trends, and associated risk factors. It also discusses prevention strategies, and the importance of early detection and highlights resources related to diagnostic and referral pathways for oral cancer across Canada.

We hope this work serves as a resource for anyone seeking to deepen their oral cancer knowledge. We thank the NCOHR oral cancer group members for their valuable comments and diligent responses to various reviews and for helping us produce this document.

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1. CANCER

Cancer is a complex and multifaceted disease characterized by the uncontrolled growth and division of abnormal cells, which leads to the development of tumours. (1) Cancers can arise from different types of cells and can occur in any anatomic site within the body. (2) Moreover, these abnormal cells have the potential to invade nearby tissues and organs. They can also spread to distant parts of the body through the bloodstream or lymphatic system, a process known as metastasis.

2. ORAL CANCER

Oral cancers are a group of malignant neoplasms developing in the mucosal epithelium of lips, oral cavity (tongue, gums, floor of the mouth, palate, and other unspecified parts of the mouth), and back of the throat, known as the oropharynx. (3) Despite being grouped as a single entity, mucosal lip, oral cavity, and oropharyngeal cancers are distinct groups of oral cancers that generally have different epidemiological profiles. Histologically, more than 90% of oral cancers are squamous cell carcinomas (4) originating in the epithelial cells that form the surface lining tissue.

Tumour stage and grade are essential factors in understanding the severity and prognosis of oral cancers. Tumour staging describes the extent of cancer spread in the body, including the size of the primary tumour and whether it has spread to nearby lymph nodes or other organs of the body.^(5, 6) The TNM staging, the most common oral cancer staging system given by the American Joint Committee on Cancer (AJCC), includes the size of the tumour (T), regional lymph node involvement (N), and evidence of spread or metastasis (M) (Table 1).^(7, 8) The size of the tumour (T) is rated from 1 to 4, with a larger number indicating a larger size. Lymph node involvement (N) is rated from 0 (no spread to nearby lymph nodes) to 3 (maximal spread to lymph nodes), and Metastasis (M) has two ratings, 0 indicating no tumour spread, and 1 indicating tumour spread in the body. TNM staging includes stage 0, followed by I to IV, with higher staging indicating more cancer spread. Stage IV is further divided into IVA, IVB, and IVC. Staging helps determine the most appropriate treatment approach and predicts the likelihood of cancer recurrence.

Table 1: Oral Cancer Staging		
Stage	TNM	Description
0	Tis, N0, M0	Tis = Carcinoma in situ (localized; non-invasive)
		NO = No regional lymph node metastasis
		M0 = No distant metastasis
T	T1, N0, M0	T1 = Tumour ≤ 2 cm with depth of invasion (DOI) ≤ 5mm.
II	T2, N0, M0	T2 = Tumour \leq 2 cm with DOI >5 mm or tumour >2 cm and \leq 4 cm with DOI \leq 10 mm.
III	T3, N0, M0 Or T1, T2, T3, N1, M0	T3 = Tumour >2 cm and ≤4 cm with DOI >10 mm or tumor >4 cm with DOI ≤10 mm. N1 = Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and no extranodal extension ENE(–).

1\/ /	T42 NO N1 N40	T42 - Moderately advanced local disease. Tumour > 4 cm with DOL
IVA	T4a, N0, N1, M0	T4a = Moderately advanced local disease. Tumour >4 cm with DOI
	Or	>10 mm or tumor invades adjacent structures only (e.g., through
	T1, T2, T3, T4a, N2, M0	cortical bone of the mandible or maxilla or involves the maxillary sinus or skin of the face).
		N2 = Metastasis in a single ipsilateral lymph node \leq 3 cm in greatest dimension and ENE(+); or >3 cm but \leq 6 cm in greatest dimension and ENE(-); or metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE(-); or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension, and ENE(-).
IVB	Any T, N3, M0	N3 = Metastasis in a lymph node >6 cm in greatest dimension and
	Or	ENE(-); or metastasis in a single ipsilateral node >3 cm in greatest
	T4b, Any N, M0	dimension and ENE(+); or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+); or in a single contralateral node of any size and ENE(+).
		T4b = Very advanced local disease. Tumor invades masticator space,
		pterygoid plates, or skull base and/or encases the internal carotid
		artery.
IVC	Any T, Any N, M1	M1=Distant metastasis

AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017

By contrast, tumour grading describes how cancer tissues appear compared to normal healthy tissues under a microscope. (6) If the cancer closely resembles normal tissue, it is called "differentiated" or a "low-grade tumour". Conversely, if the cancerous tissue looks significantly different from healthy tissue, it is described as "poorly differentiated" or a "high-grade tumour" (Table 2). Typically, a lower grade indicates favourable treatment outcomes.

Table 2: Oral Cancer Grading	
Grade	Description
Gx	Grade cannot be evaluated
G1	Cells look more like normal tissue and are well differentiated
G2	Cells are moderately differentiated
G3 and G4	Cells are poorly differentiated and do not resemble normal tissue

AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017

3. ORAL CANCER INCIDENCE AND MORTALITY IN CANADA

Over the past 25 years, there has been an increase in the oral cancer incidence in Canada. According to 1994 statistics, Canada recorded 2,005 new oral cancer cases across all provinces that year. (9) By 2021, this number had risen to 3,495, (9) including data up to 2017 for Quebec and 2019 for Nova Scotia. Since 2021, Canadian Cancer Statistics has adopted a broad category, providing data on oral cancer under the group of Head and Neck cancer (HNC). Currently, HNC is the tenth most common cancer in Canada overall, eighth among males, and thirteenth among females. (10)

Importantly, the projected number of new HNC cases in Canada for 2024 is five times that projected for cervical cancer (8,100 vs. 1,600), $^{(11)}$ and the expected number of HNC-related deaths is 2,100. This upward trend is anticipated to continue; by 2050, it is estimated that there will be 6,923 new oral cancer cases (4,629 males and 2,293 females), $^{(12)}$ with 2,230 oral cancer-related deaths (1,413 males and 817 females). (Figures 1-4)

Estimated number of new oral cancer cases Years

Figure 1: Estimated number of new oral cancer (lip, oral cavity, oropharynx) cases from 2022 to 2050, both sexes, age (0-85+), Canada

Globocan 2022

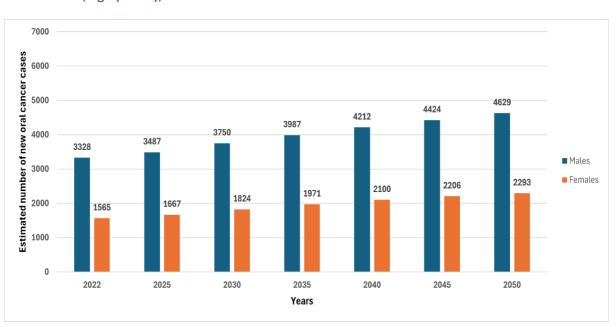


Figure 2: Estimated number of new oral cancer (lip, oral cavity, oropharynx) cases by sex from 2022 to 2050, age (0-85+), Canada

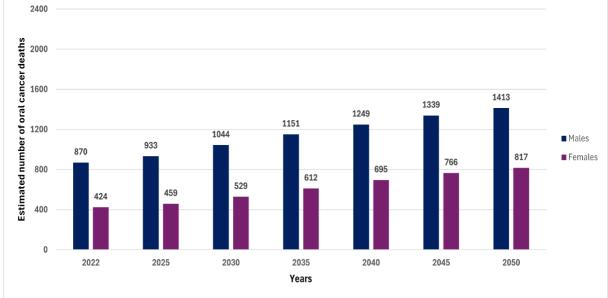
Globocan 2022

Estimated unmper of oral cancer deaths
1600
1200
800
400 Years

Figure 3: Estimated number of oral cancer (lip, oral cavity, oropharynx) mortality from 2022 to 2050, both sexes, age (0-85+), Canada.

Globocan 2022





Globocan 2022

Figures 5 and 6 further illustrate the projected trends by oral cancer subsites up to 2050. For a depiction of sex-specific trends, please refer to Appendix Figures 7-10.

Age Standardized Incidence Rates in Canada upto 2051 7.00 5.95 5.86 5.74 5.75 6.00 5.62 5.55 5.49 Age Standardized Incidence Rates 5.00 (per 100,000 person) 00°8 00°8 3.29 3.27 3.16 2.94 3.11 →Oral cavity 3.04 2.98 ---Oropharynx 2.96 2.95 2.95 ▲ All other oral regions 2.90 3.09 2.79 2.64 2.00 1.00 0.00 2022 2025 2030 2035 2040 2045 2050 Years

Figure 5: Age-standardized incidence rates by oral cancer subsite, both sexes, all ages, from 2022 to 2050, Canada

OncoSim, Canadian Partnership Against Cancer

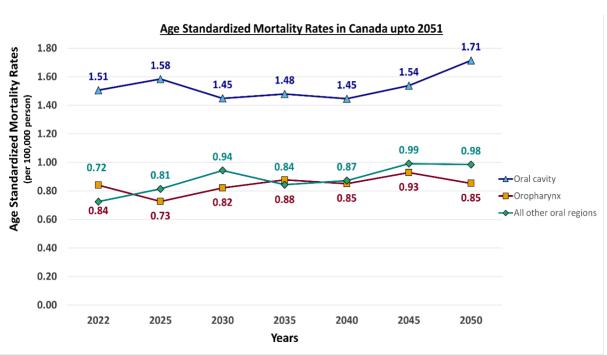


Figure 6: Age-standardized mortality rates by oral cancer subsite, both sexes, all ages, from 2022 to 2050, Canada

OncoSim, Canadian Partnership Against Cancer

The increase in oral cancer rates and projections is primarily attributed to human papillomavirus (HPV) infection^(14, 15), which preferentially affects the oropharynx, including the base of the tongue, tonsils, and soft palate. The anatomy of these regions (crypts and irregular surfaces of the tonsils) and a high concentration of lymphoid tissue in the base of the tongue create a favourable environment for HPV infection to persist. According to the HPV-related disease report, the prevalence of HPV-related oral cancer in Canada between 1993 and 2003 in both sexes ranged from 5.9% (95%CI=4.0-8.6) to 43.5% (95%CI=25.6-63.2).⁽¹⁶⁾ Notably, the incidence rates per 100,000 for HPV-related oral cancer in Canada in 2020 were 5.42 for males and 1.22 for females, with mortality rates of 1.85 for males and 0.60 for females.⁽¹⁶⁾ These cancers have reached epidemic proportions in North America, leading some researchers to refer to the rise of HPV-related cancers as 'a virus-related cancer epidemic'.⁽¹⁷⁾ The incidence now surpasses the annual incidence and mortality of cervical cancers – the most well-known HPV-related cancer – in North America.⁽¹⁸⁾

4. ORAL CANCER SURVIVAL IN CANADA

While oral cancers are mostly preventable, and there have been therapeutic advancements in recent decades, the 5-year survival rates for these malignancies remain low, around 50-60%. (19, 20) In Canada, oral cancer survival is not reported separately but is included in a broader category of HNC. The 5-year net survival for HNC in Canada is 64%. (21)

Survival of oral cancer patients is associated with the stage at cancer diagnosis and the oral cancer subsite location. Survival can be significantly improved if diagnosed in early clinical stages and when treatments are most accessible and effective. Table 3 displays 5-year survival rates by stage and location of oral cancer. (22)

Table 3: 5-year relative oral cancer survival by stage and cancer subsite				
Stage	Lip	Tongue	Floor of mouth	Oropharynx
Early stage or localized (Stage 1 or 2)	93%	78%	75%	59%
Locally advanced or regional (Stage 3, 4A or 4B)	48%	63%	38%	62%
Metastatic (Stage 4C)	52%	36%	20%	29%

Canadian Cancer Society. Survival statistics for oral cancer 2019; American Cancer Society. Survival rates of oral cavity and oropharyngeal cancer 2016

Lip cancers have a higher survival rate of over 90% when detected at an early stage. (22) This is because they are easily detectable, and their treatments are relatively accessible. Furthermore, the five-year survival rate for early-stage and localized oral cancers is higher than for advanced stages. (22) Moreover, patients with HPV-positive oral cancers have significantly higher survival rates compared to HPV-negative patients, although these cancers are usually detected at a late stage. (17) The improved survival rates among HPV-positive patients can be partly attributed to the demographic characteristics of these patients, who tend to be younger. (17) Younger patients are generally more resilient and may respond more favourably to treatments than older, HPV-negative patients. (17)

5. CAUSES AND RISK FACTORS OF ORAL CANCER

Similar to most cancers, the onset of oral cancer is intricately linked to the interplay of multiple risk factors, including health conditions, lifestyle behaviours, and exposure to specific substances. Below, we describe the risk factors for oral cancers, focusing on the major ones: tobacco use (smoked or smokeless forms), alcohol consumption, and the presence of HPV infection. (23, 24)

5.1. Smoked Tobacco: Cigarette, Bidi, Pipe, and Cigar

Tobacco smoking, a major oral cancer risk factor, includes various forms such as conventional cigarettes, cigars, bidis, pipes, and hookah. (25) Its consumption varies by geographic region and population groups. Cigarettes, cigars, and pipes are the main types of smoked tobacco in Western countries (e.g., Canada, USA, UK, Australia), while other traditional smoked forms, such as bidi, are more prevalent in the Asian continent and immigrant communities in Canada.

Several aspects of smoking behaviours impact oral cancer risk, including smoking intensity and duration, filters used, and combination with other ingredients. For example, intensity, duration of tobacco smoking, and cumulative pack-years - a measure combining these two factors, are associated with an increase in oral cancer risk in a dose-dependent fashion. (26) Similarly, tobacco users also have a higher oral cancer-associated mortality rate compared to non-tobacco users. (27) This risk augments with the increase in the amount and frequency of tobacco smoked per day. (28) The risk reduces to the level of a non-smoker 10 years after smoking cessation. (26)

5.2. Smokeless Tobacco

There is sufficient evidence supporting the carcinogenicity of smokeless tobacco. (29) The International Agency for Research on Cancer (IARC) has recognized a minimum of 28 established carcinogens present in smokeless tobacco products, among which tobaccospecific nitrosamines play a crucial role as the primary agents causing cancer in cigarettes. (29, 30) Smokeless tobacco comprises various unburned tobacco products for oral or nasal use. Chewing betel quid (a mixture of areca nut, slaked lime, and betel leaf, with or without tobacco) is one of the most common forms of smokeless tobacco and a major independent risk factor for oral cancers. (31) This habit is common among South Asian immigrants in Canada. (32)

5.3. E-cigarettes

E-cigarettes, also known as 'e-cigs,' 'vapes,' e-hookahs,' 'vape pens,' 'electronic nicotine delivery systems (ENDS)' or 'modified vape devices (MODs)', are battery-operated devices designed to simulate the experience of smoking cigarettes without the use of tobacco. (33) They contain e-liquid solutions that are heated and inhaled upon use.

Initially perceived as a less harmful alternative to tobacco, current evidence suggests that ecigarettes could potentially increase oral cancer risk. (34, 35) These devices often contain nicotine, (33) the addictive substance found in tobacco, alongside carcinogenic compounds such as trace metals, tobacco alkaloids, and phenolic compounds. (36) Notably, e-liquids that

are flavored, especially with menthol, are even more harmful to oral tissues than non-flavored e-liquids. (37)

Although some studies indicate that e-cigarettes can be an effective smoking cessation aid, (38) e-cigarettes have not been approved by the Food and Drug Administration (FDA) for this purpose. (35) Moreover, studies have suggested a positive association between tobacco smoking and e-cigarette smoking, (39) with current e-cigarette users having 54% higher odds of becoming tobacco users and current tobacco users having 43% higher odds of using e-cigarettes prospectively in Canada. (39) Indeed, most e-cigarette smokers are current or former tobacco smokers. This association can further elevate oral cancer risk. Importantly, the adverse long-term effects of e-cigarette smoking are not thoroughly understood (33) and will become apparent after several years. (35)

Unlike cigarettes, which smokers can easily quantify (e.g., counting the number of cigarettes smoked per day), creating equivalent measures for e-cigarette use has been complex due to the variety of devices, liquid types, and user habits. (40) Consequently, people might actually smoke more with e-cigarettes compared to conventional cigarettes. It is a major global concern that these products are growing in popularity, especially among young adults.

5.4. Cannabis

Due to the increased accessibility of cannabis following its legalization in Canada in 2018,⁽⁴¹⁾ it is essential to assess the cancer hazards of cannabis consumption. Epidemiological studies investigating the association between marijuana use and HNC development have yielded inconsistent results. While some studies have suggested that cannabis smoking increases oral cancer risk,^(42, 43) others have shown a protective effect of marijuana on HNC overall ^(44, 45). For example, results from the INHANCE consortium pooled analysis have shown a protective effect on tongue cancer risk.⁽⁴⁵⁾ However, the prevalence of marijuana smoking was low in most of the studies included in the pooled analysis.⁽⁴⁵⁾

Disentangling the effects of cannabis smoking is not easy, as some people prepare their marijuana joints using a mixture of marijuana and tobacco. Moreover, marijuana products can vary widely in their chemical composition, including levels of cannabinoids and other potentially carcinogenic compounds. Furthermore, the co-occurrence of risk factors, (45) such as tobacco smoking and alcohol consumption, further complicates the assessment of cannabis's impact on oral cancer risk. Additional research is needed to clarify the role of marijuana in oral cancer development. The legalization of this substance in some populations (e.g., Canada, and some USA states) should facilitate conducting studies with larger samples and less reporting bias.

5.5. Alcohol

Alcohol consumption and oral cancer risk have a dose-dependent association. (46, 47) Moderate to heavy drinkers (1 to 4 drinks per day in men, 1 to 3 drinks per day in women) have nearly twice the risk of developing oral cancers compared to non-drinkers, while heavy drinkers' (greater than 5 drinks per day in men and greater than 4 drinks per day in women) risk increases 5-fold compared to non-drinkers. (46, 47) Furthermore, individuals who consume alcohol at these levels and use tobacco are at an even higher risk for these cancers; alcohol

consumption facilitates the entry of tobacco's carcinogenic molecules into the exposed oral mucosa cells, resulting in the combined impact of these two risk factors being greater than the sum of their effects and may even exceed a multiplicative effect. (23, 48) Quitting alcohol consumption decreases oral cancer risk, which diminishes with longer periods of abstinence. (49) Importantly, current evidence suggests that no amount of alcohol is safe concerning both oral cancer and an individual's general health. (50, 51, 52)

5.6. Human Papillomaviruses (HPVs)

HPVs are sexually transmitted viruses, with a closed-circular, double-stranded DNA.⁽⁵³⁾ They are well-recognized carcinogens, contributing to approximately 4.5% of all cancer incidence worldwide.⁽⁵⁴⁾ These viruses usually infect the basal layer of epithelial cells. The majority of HPV infections are transient and may spontaneously resolve without treatment.⁽⁵⁵⁾ Yet, if the infection persists, it can lead to the development of cancer.

There are 231 established genotypes⁽⁵⁶⁾ that are divided into five genera. (57,58) Among the HPV genera, alpha (α), also known as mucosal viruses, infects a variety of different anogenital and upper aerodigestive tract mucosa and has been further classified according to their carcinogenic potential into "low-risk" (e.g., HPV-6, HPV-11) and "high-risk" (e.g., HPV-16, HPV-18). (58) Low-risk HPV can lead to benign lesions (e.g., genital warts, laryngeal papilloma). In contrast, the high-risk types, notably HPV-16, are strongly associated with oral cancers. (59,60) Beta (β) and gamma (γ), the cutaneous types, which are known to infect the oral cavity and oropharynx, have also been detected in the oral cavity and associated with oral cancer. (59,61,62,63)

As previously alluded, these viruses have been responsible for a substantial increase in oral cancer incidence, (14, 64, 65) particularly in the oropharynx. (16, 66, 67) The rise in HPV-related oral cancers can be attributed to changes in sexual behaviours in the general population such as an earlier onset of sexual activity, increased number of sexual partners, not using barrier methods such as condoms during sexual activity, and oral and anal sex behaviours. (68, 69) These tumours are significantly associated with men and the younger population. (64, 70, 71) However, the understanding of the etiological role of HPV on oral cancer remains limited, requiring further research, including patterns and implications of co-infection with different HPV types in the oral cavity.

5.7. Oral Health Status and Behaviours

Oral health status and behaviour have been associated with oral cancer risk. Systematic reviews have shown positive associations between periodontal diseases and oral cancer.^(72, 73) Similarly, results from a pooled analysis using a composite score based on oral hygiene conditions and behaviours (e.g., denture wear, gum disease, greater or less than 5 missing teeth, frequency of dental visits, and tooth-brushing frequency) reported a strong association between suboptimal oral hygiene and an increased risk of oral cancers.⁽⁷⁴⁾ Interestingly, the magnitude of the effects among all sites of the head and neck was high for the associations between oral hygiene scores and oral cavity cancers, supporting the potential causal role of oral health status.⁽⁷⁴⁾ The underlying biological mechanism for these associations is not well understood, yet oral microbiome composition may partly explain these associations.⁽⁷⁵⁾

5.8. Prolonged Exposure to the Sun

Excessive exposure to the sun can increase the risk of developing skin cancer in the head and neck region and lip cancer. Many lip cancer patients have outdoor jobs that expose them to the sun for long periods, such as that of farmers. (76) In most cases, the lower lip is impacted, likely due to its increased exposure to the sun compared to the upper lip. (76, 77)

5.9. Diet and Nutrition

There is sufficient evidence to support the association of oral cancer with diet and nutrition. Obesity, diets high in inflammatory (Dietary Inflammatory Index- DII) foods such as red meat, sugar-sweetened beverages, processed meats, and *mate*, a traditional South American drink, are associated with an increased risk of oral cancer. (78, 79, 80, 81) A pooled analysis showed that a decrease in diet quality, measured by diet quality score (DQS), by one standard deviation corresponds to a 26% increase in oral cancer risk according to the Healthy Eating Index 2005 (HEI-2005), a 14% increase with the Mediterranean Diet Score (MDS), and a 16% increase with the modified MDS for HNC (MDS-HNC). (80)

Conversely, diets rich in non-starchy vegetables, adherence to healthy dietary patterns, and coffee consumption may lower oral cancer risks. Encouraging the intake of anti-inflammatory foods might be an effective approach to prevention. Evidence shows that antioxidants, abundant in fruits and vegetables, can counteract many carcinogenic tobacco and alcohol by-products. However, there is no conclusive evidence regarding the carcinogenic potential of other diet components (such as cereals, animal fats, fish, and eggs, among others), physical activity, and height.

5.10. Age and Sex

Oral cancer is rare in younger individuals; its risk increases with age and is highest after 45 years.⁽²³⁾ However, due to the recent surge in HPV infections, oral cancers now occur more frequently in younger patients.⁽⁸⁵⁾ Among those under 50 years, HPV infections (especially HPV-16) are replacing tobacco and becoming the primary cause of cancers in the oropharynx, base of the tongue, and posterior oral cavity.⁽⁸⁶⁾

Men are more susceptible to oral cancers than women, with the ratio of affected men to women changed from 6:1 in the 1950s to around 2:1 by 2002. The ratio of HNC among Canadian men compared to Canadian women was 2.6:1 in 2021. This change is estimated to be due to the increasing number of female smokers over the last few decades.

5.11. Family history

History of HNC in a first-degree relative (parent, sibling, or child) has been associated with oral cancer risk with the risk being higher in those individuals who used alcohol and smoked tobacco. (91) However, evidence from genetic epidemiology studies, such as genome-wide association studies, remains limited in establishing a clear genetic predisposition to HNC, suggesting that familial risk may be influenced more by shared lifestyle factors than by inheritable genetic variants. (92)

6. INEQUALITIES IN ORAL CANCER

Disparities in incidence and mortality from oral cancers across different countries, including Canada, and different population groups, are major challenges that have resisted intervention efforts. The underlying reasons are complex and involve health literacy, risk behaviour patterns, access to health care, and quality of medical care.

There is strong evidence that oral cancer incidence is socially patterned; that is, individuals at the top of the social gradient have a lower risk compared to those who are low on the social scale. (93) A high incidence of oral cancers has been reported among those in low-income groups and those with a low education level, with the strongest effect among those living in countries with high-income inequalities. (94) Disadvantageous socioeconomic position (SEP) across the individual's life course further increases oral cancer risk, (93, 95, 96), with SEP in childhood potentially having a more significant impact on the risk of disease than other periods. Importantly, these associations are not entirely explained by the main oral cancer risk factors, tobacco, and alcohol. (94, 95)

Oral cancer incidence is also significantly higher among Indigenous people, with a pooled incidence rate of 13.4 per 100,000 person-years, compared to 7.2 for non-Indigenous groups. However, a Canadian report using 1992 to 2009 data showed no significant differences in the age-standardized oral cancer incidence between First Nation men and non-Indigenous men, as well as between First Nation women and non-Indigenous women. (98)

Marked disparities have also been observed in oral cancer survival rates. People living in developing countries have a much lower oral cancer survival rate than those living in developed countries. (99) Moreover, the Canadian First Nations and those living in rural populations have poorer survival outcomes compared to non-Indigenous people and those living in the cities. (100, 101)

7. IMPACT OF ORAL CANCER

Oral cancers can significantly impact patient's quality of life, presenting significant challenges to their overall health and well-being. These challenges extend beyond the physical symptoms, affecting psychological health and imposing financial strains due to the costs of treatment and work interruptions.

7.1. Individual Consequences

Individuals with oral cancer may face a significant negative impact on their health-related quality of life (HR-QoL). The adverse effects of oral cancer can result from the physical deformities and functional loss brought on by the advancement of the malignancy, as well as the detrimental side effects of treatments such as radiotherapy, chemotherapy, and surgical procedures to remove the cancerous lesion. (102)

Patients who undergo oral cancer treatment may experience changes in their normal facial appearance, which can affect their self-esteem. They may face challenges such as disfigurement, limited oral functions (e.g., speaking, swallowing, and eating abilities), stigma, social isolation, loss of sense of identity, embarrassment, depression, and psychological

distress.⁽¹⁰³⁾ Speech, voice, and swallowing functions might also be adversely impacted by mucositis and dry mouth caused by radiotherapy and chemotherapy, as well as surgical removal of structures of the tongue, palate, and lips.⁽¹³⁾

Rehabilitation is essential after cancer therapy. Reconstructive surgery can help mitigate the adverse effects of oral cancer treatment on the function and appearance of the orofacial complex. However, the tissue reconstructions can disrupt the proper functioning of facial tissues and render tasting, eating, swallowing, speaking, and hearing difficult, negatively impacting patients' quality of life, daily enjoyment, and well-being. Rehabilitation therapies, including speech therapy, physical therapy, and counselling, are essential to help an individual recover from the side effects of treatment and improve quality of life.

Anxiety is another factor that negatively affects the quality of life of oral cancer patients. It arises from several sources: the possibility of cancer progression, the uncertainty of cancer treatment effectiveness, and the fear of cancer relapse. Furthermore, these patients often face substance dependence (e.g., tobacco, alcohol) or use of opioids to alleviate the often intense pain associated with their condition. This dependency is often reinforced by the belief that quitting won't markedly improve their prognosis.

Due to a combination of the above factors, oral cancer patients often have an increased risk of depression, which can negatively impact their quality of life and interfere with their therapy and recovery process. Notably, suicide rates are markedly higher among oral cancer patients compared to the general population or individuals with other types of cancers. Most suicides occur within the first 5 years of diagnosis and are attributed to the detrimental effects of the disease on patients' quality of life. Among survivors, psychological distress may last for decades after successful treatment. 1212

7.2. Economic Consequences

Oral cancers stand out as a significant financial challenge, ranking among the most expensive solid tumours to treat. In Canada, which has a public health care system, the estimated societal impact of cancer in 2021 was projected to be approximately CAD 26 billion, with approximately one-third of this burden borne by patients and their families. Specifically for oral cancers, the estimated direct health system costs were around CAD 453 million, focusing solely on inpatient care expenses. However, it's crucial to recognize the broader impact, as these cancers incur major indirect costs on families, communities, and society.

Out-of-pocket costs, including expenses for drugs/supplements, home care, equipment, and other patient-incurred expenses, were estimated at 70 million CAD in 2021. Additionally, the estimated direct time costs associated with travel, waiting for care, and receiving treatment amounted to around CAD 46 million. Indirect costs, reflecting estimated lost earnings from employment from the patient's perspective, reached approximately CAD 84 million. Collectively, these out-of-pocket, direct, and indirect costs impose a substantial economic burden on patients, their families, and society.

The profound impact on financial circumstances has led to the recognition of cancer-related out-of-pocket spending as "financial toxicity." (115, 116) Notably, only 48% of oral cancer survivors reportedly return to work after treatment. (117) Moreover, many families affected by

cancer experience financial difficulties,⁽¹¹⁸⁾ which are likely to be greater for oral cancer survivors, considering their high rate of unemployment.⁽¹¹⁷⁾

8. EARLY DETECTION ON ORAL CANCER OUTCOMES

Early detection plays a crucial role in preventing the heavy burden of oral cancers and their mortality. Early detection not only facilitates less aggressive treatments but also significantly improves the prognosis, survival rates, and quality of life of patients. Moreover, late detection of oral cancer can impact patients' quality of life and result in psychological consequences and complications in the head and neck region. When diagnosed in the early stage, individuals with lip, tongue, and floor-of-the-mouth cancer have 5-year survival rates of 93%, 78%, and 75%, respectively. However, when diagnosed in advanced stages, these rates decline to 48% for lip, 63% for tongue, and 38% for floor-of-the-mouth cancer (Table 3). Importantly, early detection is more cost-effective for families and the healthcare system, as treatments are less burdensome compared to advanced-stage diagnoses.

In Canada, data up to June 2018 revealed that about 53% of oral cancer cases were detected at an advanced stage nationally. While province-specific reports are unavailable throughout Canada, in Alberta, 45.2% of oral cancer cases were diagnosed at stage IV between 2005 and 2017. This prevalence of late-stage detection significantly limits treatment options and complicates efforts to prevent fatal outcomes.

9. CARE PATHWAYS AND TREATMENT DELAYS

A care pathway is a structured approach followed by healthcare providers to manage and treat patients with oral cancer. It outlines the steps involved in the patient's care, from diagnosis to treatment and follow-up. Minimizing delays along this pathway is essential to improve the success of oral cancer treatment and ultimately improve patient outcomes.

Several factors can cause delays in the referral process. These delays can be classified into patient-related factors, healthcare provider-related factors, and health system-related factors.

Patient delay, the interval between a patient's initial discovery of a change in their oral cavity and presentation to a healthcare professional, (123) is the most significant contributor to the overall diagnostic delay. (124) The mean delay time varies among different populations; studies in Canada have reported a mean delay of approximately 21 weeks between the time of the appearance of the first symptoms and the patient's first visit to the health professional. (125, 126) The reasons for patient delays are poorly understood and speculative. (127) However, psychosocial factors such as the patient's previous experience with cancer, their preoccupation with life events, and self-medication or treating the lesion with over-the-counter medications may contribute to patient delay. (124) Moreover, patient's lack of awareness of the care-seeking pathways, (101, 128) provider's oversight, and prolonged lack of access to care (128) are important factors that can cause delays in receiving oral cancer care. Increasing awareness in the general population regarding recognizable signs and symptoms of lesions and when to visit a healthcare professional can, therefore, help reduce patient delays. (125, 129)

Although there is no consensus regarding the definition of professional delay, it can be generally described as the time delay between a patient's first visit to a healthcare provider and the definitive histopathological diagnosis of oral cancer, referral to a specialist, or the onset of therapy. (123, 124, 126) Some factors contributing to professional delay include healthcare providers' unnecessary referrals, misdiagnoses, prolonged wait times for imaging and biopsy, and professionals' lack of awareness of the signs and symptoms of oral cancer. (130)

Another factor that can cause diagnostic delays but does not fit in the patient-professional binary is accessibility, which is defined as "the ability to obtain services based on the patient's health needs" (131) These are health-system-related factors, and while the lack of accessibility may contribute to patient delay, it is a problem at the systems level and should not be characterized as patients' responsibility. (129)

10. CANADIAN ORAL CANCER PREVENTION PROGRAMS AND POLICIES

Creating supportive environments through programs and policies can be a more effective strategy for preventing cancer and enhancing population health than approaches targeting individuals. Policies usually have a broader reach as they target the whole population. They also reduce the need for initiatives targeted toward specific groups, such as underserved populations. Programs and policies aiming to prevent oral cancer can generally be divided into two categories:

- (i) Programs and policies that target the risk factors of oral cancer:
- (ii) Programs and policies specifically targeting oral cancer.

10.1. Programs and Policies Targeting Oral Cancer Risk Factors

They target oral cancer risk factors, including HPV, tobacco, and alcohol consumption. Targeting risk factors will not only reduce oral cancer risk but also reduce the risk of many chronic diseases, including other cancers. Following are the programs and policies targeting oral cancer risk factors in Canada.

Human papillomavirus (HPV)

Although the effect of HPV vaccination on oral cancer incidence is not yet clear, projected estimates indicate that by 2045, we will observe a significant reduction in oral cancer rates among vaccinated younger and middle-aged adults. (132) Canada aims to achieve 90% HPV vaccination coverage by 2025 for adolescents under 17 years of age, (133) the target age for HPV vaccination before adolescents engage in sexual activity, (55) as the vaccines are most effective before exposure to the virus. (134) Improvement in vaccination rates is expected to impact further the incidence of these cancers. (132)

Canada offers two HPV vaccines to prevent HPV infections: the bivalent HPV vaccine (2vHPV vaccine), Cervarix (GSK), which protects against HPV subtypes 16 and 18, and the nine-valent HPV vaccine (9vHPV vaccine), Gardasil 9 (MERCK), which protects against nine subtypes-HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58. (135) Both vaccines cover HPV subtypes 16 and 18, which account for roughly 70% of cervical and oral cancer cases. (135). While 2vHPV and 9vHPV

vaccines are available in Canada, the Government of Canada recommends the 9vHPV HPV vaccine as it covers additional HPV subtypes, extending its efficacy to a wider range of cervical and oral infections. (135)

To ensure widespread coverage, HPV vaccines are made available for both boys and girls through two publicly funded initiatives:⁽⁵⁵⁾

- (i) School-based Immunization Programs: The 9vHPV vaccine is offered to school-aged boys and girls through school-based immunization programs in all provinces and territories.

 (136)
- (ii) Catch-up HPV Immunization Programs: Available for individuals who missed school-based programs or were not in school during the vaccine introduction. (55) These catch-up programs usually target individuals aged 18 to 26 who do not require parental consent. (55)

In most Canadian provinces, individuals over 26 are not covered by these programs, except for specific exceptions (e.g., Manitoba's HPV catch-up program covers high-risk females with immunodeficiency up to 45 years of age). (55) Therefore, adults seeking HPV immunization who were not covered by the publicly funded school HPV vaccination programs or catch-up programs must actively seek vaccination themselves or have it recommended by a health professional. These vaccines are expensive, and although some people are covered through private insurance, this cost can be a barrier for some people. (55, 137)

Tobacco Consumption

Canada's Tobacco Strategy (CTS) is the national approach to combat tobacco consumption, aiming to reduce tobacco use to under 5% by 2035. To achieve this, there are various policies targeting tobacco consumption in Canada.

- i. Smoke-Free Places: Under the Non-smoker's Health Act, (139) there are smoking restrictions in workplaces and public places to protect people from exposure to tobacco smoke. This includes banning smoking in virtually all indoor public places and workplaces.
- ii. Tobacco Packaging and Labelling: Tobacco Product Appearance, Packaging and Labelling Regulations (TPAPLR) is adopted under the Tobacco and Vaping Products Act in 2023, which includes the first regulation in the world currently to require health warnings not only on the package but directly on tobacco products (cigarettes, cigars with tipping paper, tubes, cigarettes without tipping paper). They also include health messages on the inside of the tobacco packages. (140, 141)
- iii. Cigarette Contents and Disclosures: Under Canada's Tobacco Reporting Regulations, manufacturers and importers are required to submit detailed reports to Health Canada on tobacco products and emissions, covering sales, ingredients, production, promotions, and research. The legislation restricts certain ingredients in cigarettes, such as prohibiting the use of sugars, sweeteners, menthol, mint, spearmint, spices, herbs, components suggesting health benefits, substances linked to energy or vitality, and colour additives. (142, 143)
- iv. Prohibitions on Tobacco Advertising, Promotion, and Sponsorship: Enforcing prohibitions on tobacco promotion, advertisements, and sponsorship, such as the cigarette display ban, which mandates stores to keep tobacco products out of sight so people would smoke less. The regulation also forbids the terms "mild", "light", and similar phrases on

- a range of tobacco products and accessories, including cigarettes, cigars, and related items.⁽¹⁴⁴⁾
- v. Sales Restrictions: Tobacco products sale is prohibited to minors (below the age of 18), and the law restricts the sale via vending machines. (145)
- vi. Provincial and Territorial Services for Quitting Smoking: Individuals can access quit coaches for counselling and guidance on smoking cessation. Each province has quitting lines available free of charge. (146) In 2022-2023, 95% (108 out of 114) of cancer care settings offered help to quit smoking compared to only 56% in 2017-2018, and 49% (56 out of 114) provided culturally appropriate support for the Indigenous communities (First Nations, Inuit, Métis peoples). (147)
- vii. Tax on tobacco products: Increasing taxes on tobacco products, leading to increased tobacco prices, aiming at reducing tobacco consumption. (148)

<u>Alcohol</u>

The federal, provincial, and territorial governments in Canada have implemented policies for tackling alcohol consumption:

- Alcohol Pricing and Tax Policies:
 - a. Alcohol Pricing: Adjusting alcohol prices and taxes is a crucial method for combating alcohol consumption and related harms⁽¹⁴⁹⁾ as higher alcohol prices correlate with reduced alcohol consumption.⁽¹⁵⁰⁾ Minimum alcohol pricing policies are prevalent in most Canadian provinces, including Newfoundland and Labrador (NL), Nova Scotia (NS), Prince Edward Island (PE), Ontario (ON), Manitoba (MB), Saskatchewan (SK), and British Columbia (BC), which have pricing regulations based on standard drinks.⁽¹⁵¹⁾ Furthermore, these provinces (except BC), have volumetric pricing policies that increase the price based on the amount purchased.⁽¹⁵¹⁾ New Brunswick (NB) uses pricing per ounce, while Alberta (AB) uses per-can, per-bottle, and per-ounce minimums, causing the price to increase in proportion to the amount purchased.⁽¹⁵¹⁾ Quebec (QC) applies minimum pricing exclusively to grocery store beer. In addition, ON has additional taxes on beer, wine, and spirits based on the amount purchased.⁽¹⁵¹⁾
 - b. Alcohol Tax Policies: Alcohol tax policies are implemented at federal, provincial, and territorial levels in Canada, and vary across territories and provinces.⁽¹⁵¹⁾ Provinces of NB, PE, SK, BC, and Yukon tax the total alcohol purchase price, while QC taxes alcohol by volume. ON taxes alcohol by both total purchase and volume.⁽¹⁵¹⁾
- ii. Marketing and advertising:

Alcohol marketing is shown to be associated with the earlier onset of drinking and heavier alcohol consumption. (152) In Canada, all provinces and territories are required to adhere to the Code for broadcast advertising of alcoholic beverages set by the Canadian Radio-television and Telecommunications Commission. This code prohibits advertisements that are directed at minors or endorse alcohol misuse, as well as those that hint at social acceptance, success, and lifestyle benefits linked to alcohol misuse. Additional policy measures also exist across various provinces and territories, such as restrictions on advertisements near elementary or secondary schools or places of worship in SK, restricting the frequency of advertisements in NB, and price promotion restrictions suggestive of low cost in ON, SK, and Northwest Territories. (151)

iii. Setting a minimum legal drinking age:

A higher drinking age delays first alcohol use and reduces heavy drinking and alcohol-related deaths in young adults.⁽¹⁵³⁾ The minimum legal drinking age in Canada is 19 years (except in Alberta, Manitoba, and Quebec provinces, where it is 18 years).⁽¹⁵⁴⁾

iv. Additional restrictions:

Various provinces and territories have implemented additional restrictions focusing on physical availability, implementation of health warning labels, alcohol sale timings, and reducing privatization of alcohol retail in varying capacities. (151)

10.2. Programs Targeting Oral Cancer

Despite numerous awareness-raising campaigns on oral cancer prevention and screening by various cancer societies and associations, there is only one organized program promoting oral cancer prevention, screening, early diagnosis, and treatment in Canada - the British Columbia Oral Cancer Prevention Program (BCOCPP). (155) The program, comprising a multidisciplinary team, focuses on detecting persons at high risk of oral cancer, establishing a provincial oral cancer screening initiative and functional referral pathways, and enhancing early detection of oral cancer lesions. (155) While the program is based in British Columbia, its activities extend beyond the province. In addition to triaging and following the high-risk populations (e.g., low socioeconomic individuals and older adults), establishing guidelines for screening and referral pathways at a provincial level, the program focuses on raising oral cancer awareness at a national and global level, as well as developing outreach initiatives in countries with a high incidence of oral cancer, such as India and China. (155)

11. KNOWLEDGE GAPS AND RECOMMENDATIONS

This report allowed the identification of several knowledge gaps on oral cancer in Canada. These gaps and related recommendations are mentioned below.

11.1. Oral Cancer Data Labelling and Availability

Over the years, the general state of data for oral cancer has improved, and more recent data are available. However, the lack of standardization in collecting and labelling oral cancer data emphasizes the need for more accurate and consistent reporting. Specifically, the classification of cancer subtypes should consider the potential etiological differences between each subtype and provide consistent and evidence-based definitions. The databases containing oral cancer data (Statistics Canada, Canadian Cancer Society, and Quebec Cancer Registry) have defined oral cancers rather variably, with some defining oral cancers under a broad category of HNCs and others as various anatomical subtypes (e.g., cancers of lip, tongue, oropharynx, hypopharynx, and other oral regions), which makes drawing causal inferences regarding subtypes of oral cancer across registries difficult. Statistics Canada has oral cancer data for most provinces up to 2020, except for Quebec and Nova Scotia. Even though oral cancer data for Quebec is available up to 2020 in the Quebec cancer registry (along with the estimated predictions), the Statistics Canada dataset provides Quebec's cancer data only until 2017. Nova Scotia's oral cancer data also exists only up to 2018. Consequently, data for oral cancer in Canada exists up to 2017 and for Canada, excluding Quebec, up to 2018.

Beyond these quantitative data gaps, there is also a lack of qualitative data on oral cancer in Canada. Qualitative research focusing on patients' and stakeholders' direct perspectives and experiences in cancer care would shed light on the nuanced realities influencing oral cancer care and patient behaviours. This type of data, typically collected through interviews, focus groups, and open-ended surveys, is invaluable for exploring the causes of oral cancer, patient experiences, treatment interactions, and the impact of care delays. Additionally, it provides insights into patients' emotional and psychological responses to their care pathways.

Addressing these issues by enhancing data collection methods and ensuring consistency in data classification will improve our understanding of the causes and impact of oral cancer in Canada. It will also help formulate targeted interventions based on reliable, comprehensive data that includes the valuable perspectives of those affected and involved in the care pathways, including health professionals and peer caregivers.

11.2. Research and Data on Indigenous Communities

While studies have reported a higher incidence of oral cancer and worse survival among Indigenous communities, the descendants of the first inhabitants of Canada, First Nations people, Métis, and Inuit, data on this population are limited. Similar to other chronic conditions, these disparities are frequently attributed to several systemic issues, including interruptions in the continuum of care, the absence of culturally appropriate treatments, and inadequate access to education and support services. To address these inequities effectively, it is imperative to adopt updated and more comprehensive research methodologies, such as community-based participatory research (CBPR). CBPR employs a collaborative approach that emphasizes equal partnership between the patients, community members, researchers, and stakeholders, making it more patient-centred and community-driven.

11.3. Research on Treatment Delays and Their Causes

While there is research on referral pathways and treatment delays worldwide, Canadian-specific studies are still limited. (128, 130, 156) More importantly, studies specific to particular populations or provinces are needed, as they provide a better understanding of the local context. These studies help identify unique regional challenges, healthcare infrastructure limitations, and population-specific risk factors.

11.4. Preventive Programs Specifically Tailored to Oral Cancer

Our report revealed that Canada's only program specific to preventing oral cancer is the Oral Cancer Prevention Program in British Columbia. (155) This program offers oral cancer statistics in the BC province and provides referrals and consolidated information guides to the patients. Additionally, the program also actively initiates oral health awareness campaigns. Such efforts may significantly contribute to educating patients, raising awareness about oral cancer risks, and informing them about the available referral pathways. To effectively reduce incidence and mortality, there is a need for additional prevention and screening initiatives nationwide. The current lack of such programs highlights the need for a more comprehensive and inclusive response to oral cancers in Canada and the need for more efforts and resources to be administered to this health issue.

11.5. Focus on High-Risk Populations Based on Risk Factors and Behaviours

Understanding the interactions of various risk factors and their differential impact on the development of oral cancers can be used for targeting individuals who are most likely to develop oral cancer. Improving oral cancer knowledge among primary health care professionals (e.g., dental hygienists, dentists, and doctors) may improve their skills in early detection and motivate them to engage in risk counselling. Moreover, using tools to evaluate individual risk assessment will assist professionals in identifying high-risk patients, allowing clinicians to indicate actual risk to their patients and engage in motivational and behavioral counselling and early treatments when necessary.

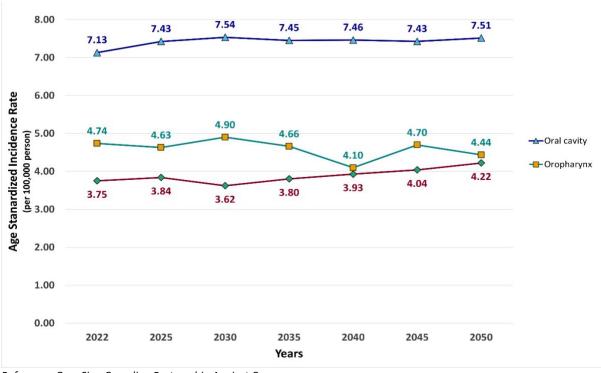
It is important to note that habit transmission, such as tobacco or alcohol use, follows an intergenerational pattern within families. (157, 158). They are often influenced by a complex interplay of social, genetic, and environmental factors. Evidence suggests that preventive interventions, such as school-based buddy programs, reduced tobacco smoking rates not only among children but also among their parents. (159) Similarly, mass media campaigns that appeal to parental morality have proven effective in addressing behaviors like tobacco and alcohol use. (160) These campaigns, which help disrupt the role modelling inherent in intergenerational habit transmission, should be maintained and expanded to further enhance public health impact among high-risk groups.

11.6. Leveraging Artificial Intelligence to Address Gaps

Artificial Intelligence (AI) presents a transformative opportunity to address the gaps in oral cancer care. (161) Integrating AI into diagnostics, predictive analysis, and treatment planning can significantly enhance the early detection of oral cancers. (161, 162) Evidence shows that AI techniques can detect oral cancers with an accuracy of over 90% using various methods⁽¹⁶¹⁾ Notably, AI can detect oral lesions in photographs with an accuracy of 75%-100%, higher than doctors, who can detect it accurately 61%-98% of the times. (163) This is extremely useful in the early and accurate detection of oral cancers and can aid healthcare professionals in beginning treatments early and improving patient survival rates. (161) AI can also be a cost-effective screening tool, as clinical images captured on mobile phones could be used to screen oral cancer before going through more expensive or invasive diagnosis techniques such as scans and biopsies. (161, 162) Additionally, AI's capability to analyze complex data sets and variables allows for identifying patterns indicating a higher risk of disease development or recurrence, enabling the development of personalized treatment strategies tailored to individual genetic profiles and disease characteristics. (164) When used ethically, AI could lead to more efficient, effective, and personalized patient management. However, it is important to highlight that AI is relatively new and has major methodological challenges; therefore more research, proper training, and collaboration among clinicians, basic scientists, engineering, and data scientists are needed before major conclusions or interventions are introduced.

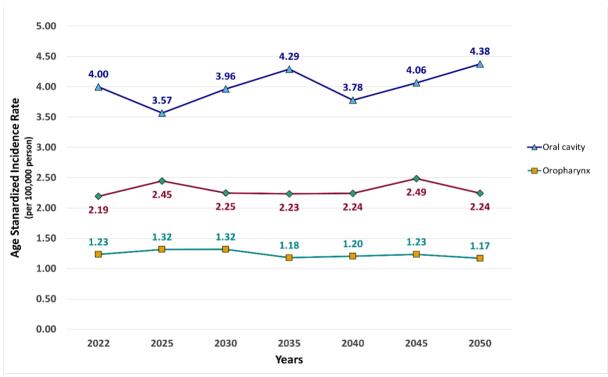
APPENDIX A: SUPPLEMENTAL FIGURES

Figure 7: Age-standardized incidence rates by oral cancer site, males, all ages, up to 2050, Canada



Reference: OncoSim, Canadian Partnership Against Cancer

Figure 8: Age-standardized incidence rates by oral cancer site, females, all ages, up to 2050, Canada



Reference: OncoSim, Canadian Partnership Against Cancer

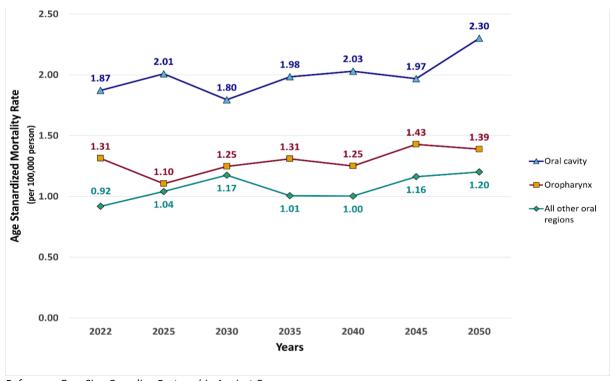
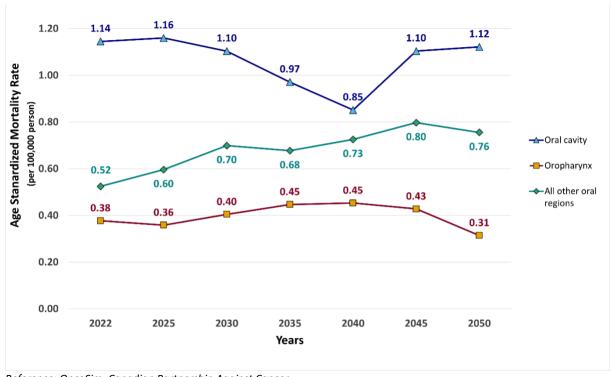


Figure 9: Age-standardized mortality rates by oral cancer site, males, all ages, up to 2050, Canada

Reference: OncoSim, Canadian Partnership Against Cancer

Figure 10: Age-standardized mortality rates by oral cancer site, females, all ages, up to 2050, Canada



Reference: OncoSim, Canadian Partnership Against Cancer

APPENDIX B: METHODOLOGY

This section explains the methodology and methods used for writing each report section.

Initial consultation with stakeholders

To develop this document, we began by consulting diverse stakeholders in one-on-one meetings, including health professionals, researchers, students, residents, and others actively engaged in the field of oral cancer. We gathered insights into their key concerns, such as oral cancer epidemiology, risk factors, existing policies, treatment pathways, and knowledge gaps in Canada. These consultations shaped the report to better support healthcare professionals and to serve as a consolidated resource for patients.

What is oral cancer?

This section was based on a rapid literature review conducted using Google and Google Scholar. The definitions on the Government of Canada and the Canadian Cancer Society websites were also used to improve the report's understanding.

Impact of Oral Cancer

A rapid literature review was conducted using Google and Google Scholar to synthesize information on the psychological and economic impacts of oral cancer and their impact on patient's quality of life. Information about the economic burden of oral cancers was also obtained from the Canadian Partnership Against Cancer website.

Importance of oral cancer screening and early detection

A rapid literature review was conducted using Google and Google Scholar to obtain information regarding the importance of early detection and screening, involving self-examination and screening by a health professional.

Causes and Risk Factors

A rapid literature review in Google and Google Scholar was conducted to identify information concerning the most common oral cancer risk factors, namely tobacco smoking, alcohol consumption, HPV, smokeless tobacco, cannabis, e-cigarettes, age and sex, and exposure to the sun. The websites of the Government of Canada and the Canadian Cancer Society were also consulted.

Referral Pathways and Treatment Delays

A rapid literature review using Google and Google Scholar was conducted to identify referral pathways in Canada and what might be causing delays in treatment. The oral cancer referral pathway maps provided by Cancer Care Ontario and the British Columbia guidelines for the early detection of oral cancer in British Columbia were also consulted. (To access the full version of Ontario pathway maps and the BC guidelines for early detection of oral cancer, please refer to Appendix C)

Canadian Oral Cancer Prevention Programs and Policies

To identify policies targeting the most important risk factors for oral cancer, namely tobacco, alcohol, and HPV, the policy packs provided by the Canadian Partnerships Against Cancer were used. (To access the full tobacco, alcohol, and HPV policy packs, please refer to Appendix C.)

A rapid review of empirical and grey literature was conducted using Google and Google Scholar to identify programs and policies targeting oral cancer. The only program identified through this search was the BC Oral Cancer Prevention Program. However, more comprehensive searches might reveal other, smaller scale programs.

Figures

This section describes the current status and trends of oral cancer in Canada, and how oral cancer trends in Canada will look in the future.

Figures 1-4: To describe how the state of oral cancer in Canada might look like in the future, predictions were made using GloboCan. The GloboCan platform does not include Quebec data.

Figures 5-10: The OncoSim platform was used. Oncosim, provided by the Canadian Partnership Against Cancer, is a model that predicts the state of 25 different types of cancer up to 2050. The OncoSim platform includes Quebec data.

APPENDIX C: Useful Links

- Referral Pathways provided by Cancer Care Ontario:
 - Ontario Oropharyngeal Squamous Cell Cancer Diagnosis Pathway Map: https://www.cancercareontario.ca/sites/ccocancercare/files/assets/DPMOropharyngealSquamousDiagnosis 0.pdf
 - Ontario HPV-positive Oropharyngeal Squamous Cell Carcinoma Treatment Pathway
 Map:
 https://www.cancercareontario.ca/sites/ccocancercare/files/assets/DPMOropharyngealPositiveTreatment.pdf
 - HPV-Negative Oropharyngeal Squamous Cell Carcinoma Treatment Pathway Map: https://www.cancercareontario.ca/sites/ccocancercare/files/assets/DPMOropharyngealNegativeTreatment.pdf
- British Columbia Oral Cancer Prevention Program:
 - BC oral cancer prevention program: http://www.bccancer.bc.ca/health-professionals/clinical-resources/oral
 - BC's guideline for early detection of oral cancer (2008):
 http://www.bccancer.bc.ca/screening-site/Documents/OC Guideline 2008.pdf
- Oral cancer risk factor policy packs (provided by Canadian Partnership Against Cancer):
 - Commercial tobacco policy pack: https://s22457.pcdn.co/wp-content/uploads/2019/06/Commercial-Tobacco-Policy-Pack-EN.pdf
 - Alcohol policy and cancer in Canada: Background and key statistics: https://s22457.pcdn.co/wp-content/uploads/2021/06/Alcohol-Background-Stats-EN.pdf
 - HPV immunization for the prevention of cervical cancer: https://s22457.pcdn.co/wp-content/uploads/2021/04/HPV-immunization-prevention-cervical-cancer-EN.pdf
- Provincial Cancer Registries in Canada
 - Ontario Cancer Registry
 - Website: https://www.cancercareontario.ca/en/cancer-careontario/programs/data-research/ontario-cancer-registry
 - Email: <u>ocrquestions@cancercare.on.ca</u>
 - British Columbia Cancer Registry
 - http://www.bccancer.bc.ca
 - Quebec Cancer Registry
 - https://www.msss.gouv.qc.ca/ministere/lutte-contre-le-cancer/
 - https://k28.pub.msss.rtss.qc.ca/Formulaires/Fichier/ListeFichierCategorie.asp
 x

- No link or contact address, but contacting them is possible through their website: https://k28.pub.msss.rtss.qc.ca/layout/NousJoindre.aspx (this is for joining them, not seeking more information).
- Email: rqc@msss.gouv.qc.ca
- o Alberta Cancer Registry
 - https://www.albertahealthservices.ca/cancer/cancer.aspx
 - Email: ahsinfo@albertahealthservices.ca
- Saskatchewan Cancer Registry
 - http://saskcancer.ca
 - Email: info@saskcancer.ca
- o Nova Scotia Cancer Registry
 - https://nshealth.ca/cancer-care
 - Email: wearelistening@nshealth.ca
- Newfoundland and Labrador Cancer Registry
 - https://cancercare.easternhealth.ca
- o Prince Edward Island
 - https://www.princeedwardisland.ca/en/information/health-pei/cancerresearch-and-surveillance
 - Email: healthpei@gov.pe.ca
- o New Brunswick
 - https://www2.gnb.ca/content/gnb/en/departments/health/NewBrunswickC ancerNetwork.html
 - Email: https://www.gnb.ca/0051/mail-e.asp
- Manitoba
 - https://www.cancercare.mb.ca/home/
 - Email: donate@cancercare.mb.ca
 - Contact number: +1-877-407-2223
- Northwest Territories
 - https://www.hss.gov.nt.ca/en
 - Link to contact: https://www.hss.gov.nt.ca/en/content/contact-us
- o <u>Yukon</u>
 - https://yukon.ca

• Email: inquiry.desk@gov.yk.ca

o <u>Nunavut</u>

• There is no cancer registry for Nunavut.

REFERENCES

- 1. National Cancer Institute. What Is Cancer? : Available from: https://www.cancer.gov/about-cancer/understanding/what-is-cancer. Accessed [October 15, 2023].
- 2. Cancer Research UK. How Cancers Grow. : Available from: http://www.cancerresearchuk.org/about-cancer/what-is-cancer/how-cancers-grow. Accessed [October 14, 2023].
- 3. National Institute of Dental and Craniofacial Research. Oral Cancer: Available from: https://www.nidcr.nih.gov/health-info/oral-cancer Accessed [22 February, 2024].
- 4. Neville BW, Damm DD, Allen CM, Chi AC. Oral and maxillofacial pathology. 5th ed: Elsevier Health Sciences; 2023.
- 5. Canadian Cancer Society. Staging of Oral Cancer Available from: https://cancer.ca/en/cancer-information/cancer-types/oral/staging. Accessed [April 24, 2024].
- 6. Canadian Cancer Society. Grading of Oral Cancer: Available from: https://cancer.ca/en/cancer-information/cancer-types/oral/grading. Accessed [April 24, 2024].
- 7. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93-9.
- 8. National Cancer Institute. Lip and Oral Cavity Cancer Treatment (PDQ®)—Health Professional Version: https://www.cancer.gov/types/head-and-neck/hp/adult/lip-mouth-treatment-pdq#section_3.4. Accessed [April 24, 2024].
- 9. Statistics Canada. Table 13-10-0111-01. Number and rates of new cases of primary cancer, by cancer type, age group and sex. DOI: https://doi.org/10.25318/1310011101-eng. 2024.
- 10. Canadian Cancer Society. Canadian cancer statistics 2024: cancer-specific stats. . 2024. Available from: <a href="https://cdn.cancer.ca/-/media/files/research/cancer-statistics/2024-statistics/2024-cmaj/2024_cancer-specific-stats.pdf?rev=-1&hash=AB4A55266C9E3E89F32D4B921451F446&gl=1*f9mu9g*gcl_au*MTQyOTA3NTO3Ni4xNzE1NDM1NTk5. . Accessed [May 5, 2024].
- 11. Brenner DR, Gillis J, Demers AA, Ellison LF, Billette J-M, Zhang SX, et al. Projected estimates of cancer in Canada in 2024. Can Med Assoc J. 2024;196(18):E615-E23.
- 12. Global Cancer Observatory. Cancer Tomorrow. Estimated number of new cases from 2022 to 2045, both sexes, age [0-85+]. International Agency for Research on Cancer. Available from:
- https://gco.iarc.fr/tomorrow/en/dataviz/bubbles?populations=124&cancers=1_3&group_cancers=1&multiple_cancers=1. Accessed [October 30, 2023].
- 13. Global Cancer Observatory. Cancer Tomorrow. Estimated number of deaths from 2020 to 2040, Mortality, Both sexes, age [0-85+]: International Agency for Research on Cancer. Available from:
- https://gco.iarc.fr/tomorrow/en/dataviz/tables?types=1&sexes=0&mode=cancer&group_popu_lations=1&multiple_populations=1&multiple_cancers=1&cancers=20&populations=124.

 Accessed [July 25, 2023].
- 14. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. J Clin Oncol. 2013;31(36):4550-9.
- 15. Simard EP, Torre LA, Jemal A. International trends in head and neck cancer incidence rates: differences by country, sex and anatomic site. Oral Oncol. 2014;50(5):387-403.

- 16. Bruni L AG, Serrano B, Mena M, Collado JJ, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in the World. Summary Report 10 March 2023. Available from: https://hpvcentre.net/statistics/reports/XWX.pdf. Accessed [May 30, 2024].
- 17. Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. Lancet Oncol. 2010;11(8):781-9.
- 18. Roman BR, Aragones A. Epidemiology and incidence of HPV-related cancers of the head and neck. J Surg Oncol. 2021;124(6):920-2.
- 19. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009;45(4-5):309-16.
- 20. Zini A, Czerninski R, Sgan-Cohen HD. Oral cancer over four decades: epidemiology, trends, histology, and survival by anatomical sites. J Oral Pathol Med. 2010;39(4):299-305.
- 21. Canadian Cancer Statistics Advisory Committee in collaboration with the Canadian Cancer Society, Statistics Canada and the Public Health Agency of Canada. Canadian Cancer Statistics 2023. Toronto, ON: Canadian Cancer Society; 2023. Available from: cancer.ca/Canadian-Cancer-Statistics-2023-EN. Accessed [December 5, 2023].
- 22. Canadian Cancer Society. Survival statistics for oral cancer. Available from: <a href="https://cancer.ca/en/cancer-information/cancer-types/oral/prognosis-and-survival/survival-statistics#:~:text=In%20Canada%2C%20the%205%2Dyear,and%20neck%20cancer%20is%2064%25. Accessed [February 24, 2024].
- 23. Canadian Cancer Society. Risk factors for oral cancer: Available from: https://cancer.ca/en/cancer-information/cancer-types/oral/risks. Accessed [June 7, 2024].
- 24. Farsi NJ, Rousseau MC, Schlecht N, Castonguay G, Allison P, Nguyen-Tan PF, et al. Aetiological heterogeneity of head and neck squamous cell carcinomas: the role of human papillomavirus infections, smoking and alcohol. Carcinogenesis. 2017;38(12):1188-95.
- 25. Ram H, Sarkar J, Kumar H, Konwar R, Bhatt MLB, Mohammad S. Oral Cancer: Risk Factors and Molecular Pathogenesis. Journal of Maxillofacial and Oral Surgery. 2011;10(2):132.
- 26. International Agency of Research on Cancer (IARC). Personal Habits and Indoor Combustions: Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 100E 2012.
- 27. Qiu J, Wen H, Bai J, Yu C. The mortality of oral cancer attributable to tobacco in China, the US, and India. J Cancer Res Clin Oncol. 2023;149(18):16741-52.
- 28. Office of the Surgeon G, Office on S, Health. Reports of the Surgeon General. The Health Consequences of Smoking: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); 2004.
- 29. International Agency of Research on Cancer (IARC). Smokeless Tobacco and Some Tobacco-specific N-Nitrosamines: Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 89. 2007.
- 30. Health Canada. Smokeless Tobacco Products: A Chemical and Toxicity Analysis. 2010. Available from: https://publications.gc.ca/collections/collection-2011/sc-hc/H128-1-10-627-eng.pdf. Accessed [October 20, 2023].
- 31. Guha N, Warnakulasuriya S, Vlaanderen J, Straif K. Betel quid chewing and the risk of oral and oropharyngeal cancers: a meta-analysis with implications for cancer control. Int J Cancer. 2014;135(6):1433-43.
- 32. Auluck A, Hislop G, Poh C, Zhang L, Rosin MP. Areca nut and betel quid chewing among South Asian immigrants to Western countries and its implications for oral cancer screening. Rural and remote health. 2009;9(2):1-8.
- 33. Centers for Disease Control and Prevention. E-Cigarettes (Vapes): Available from: https://www.cdc.gov/tobacco/e-

- <u>cigarettes/?CDC_AAref_Val=https://www.cdc.gov/tobacco/basic_information/e-cigarettes/index.htm</u>. Accessed [February 24, 2024].
- 34. Nguyen H, Kitzmiller J, Nguyen K, Nguyen C, Bui T. Oral carcinoma associated with chronic use of electronic cigarettes. Otolaryngol (Sunnyvale). 2017;7(304):2.
- 35. Szukalska M, Szyfter K, Florek E, Rodrigo JP, Rinaldo A, Mäkitie AA, et al. Electronic Cigarettes and Head and Neck Cancer Risk—Current State of Art. Cancers. 2020;12(11):3274.
- 36. Flach S, Maniam P, Manickavasagam J. E-cigarettes and head and neck cancers: A systematic review of the current literature. Clinical Otolaryngology. 2019;44(5):749-56.
- 37. Sundar IK, Javed F, Romanos GE, Rahman I. E-cigarettes and flavorings induce inflammatory and pro-senescence responses in oral epithelial cells and periodontal fibroblasts. Oncotarget. 2016;7(47):77196.
- 38. Rouabhia M. Impact of electronic cigarettes on oral health: a review. J Can Dent Assoc. 2020;86:1488-2159.
- 39. Aleyan S, Gohari MR, Cole AG, Leatherdale ST. Exploring the Bi-Directional Association between Tobacco and E-Cigarette Use among Youth in Canada. International Journal of Environmental Research and Public Health. 2019;16(21):4256.
- 40. Soule E, Bansal-Travers M, Grana R, McIntosh S, Price S, Unger JB, et al. Electronic cigarette use intensity measurement challenges and regulatory implications. Tob Control. 2023;32(1):124-9.
- 41. Justice Laws Website GoC. Cannabis Act (S.C. 2018, c.16). : Available from: https://laws-lois.justice.gc.ca/eng/acts/C-24.5/. Accessed [February 20, 2024].
- 42. Keboa MT, Enriquez N, Martel M, Nicolau B, Macdonald ME. Oral health implications of cannabis smoking: A rapid evidence review. J Can Dent Assoc. 2020;86(k2):1488-2159.
- 43. Liu C, Qi X, Yang D, Neely A, Zhou Z. The effects of cannabis use on oral health. Oral Diseases. 2020;26(7):1366-74.
- 44. Liang C, McClean MD, Marsit C, Christensen B, Peters E, Nelson HH, et al. A population-based case-control study of marijuana use and head and neck squamous cell carcinoma. Cancer Prev Res (Phila). 2009;2(8):759-68.
- 45. Marks MA, Chaturvedi AK, Kelsey K, Straif K, Berthiller J, Schwartz SM, et al. Association of Marijuana Smoking with Oropharyngeal and Oral Tongue Cancers: Pooled Analysis from the INHANCE Consortium. Cancer Epidemiology, Biomarkers & Prevention. 2014;23(1):160-71.
- 46. LoConte NK, Brewster AM, Kaur JS, Merrill JK, Alberg AJ. Alcohol and Cancer: A Statement of the American Society of Clinical Oncology. J Clin Oncol. 2018;36(1):83-93.
- 47. Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer. 2015;112(3):580-93.
- 48. McCoy GD. A biochemical approach to the etiology of alcohol related cancers of the head and neck. Laryngoscope. 1978;88(1 Pt 2 Suppl 8):59-62.
- 49. Marron M, Boffetta P, Zhang Z-F, Zaridze D, Wünsch-Filho V, Winn DM, et al. Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk. International journal of epidemiology. 2010;39(1):182-96.
- 50. Burton R, Sheron N. No level of alcohol consumption improves health. The Lancet. 2018;392(10152):987-8.
- 51. Health Do. UK chief medical officers' low risk drinking guidelines. Department of Health London; 2016.
- 52. Paradis C, Butt, P., Shield, K., Poole, N., Wells, S., Naimi, T., Sherk, A., &, the Low-Risk Alcohol Drinking Guidelines Scientific Expert Panels. Canada's Guidance

on Alcohol and Health: Final Report. Ottawa, Ont. Canadian Centre on Substance Use and

Addiction: 2023. Available from: https://www.ccsa.ca/sites/default/files/2023-01/CCSA_Canadas_Guidance_on_Alcohol_and_Health_Final_Report_en.pdf. Accessed [October 30, 2024].

- 53. International Agency of Research on Cancer (IARC). Human Papillomaviruses: Monographs on the Evaluation of Carcinogenic Risks to Humans.2007.
- 54. de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer. 2017;141(4):664-70.
- 55. Canadian Partnership Against Cancer. HPV Immunization for the Prevention of Cervical Cancer. 2021. Available from: https://s22457.pcdn.co/wp-content/uploads/2021/04/HPV-immunization-prevention-cervical-cancer-EN.pdf. Accessed [September 13, 2022].
- 56. International Human Papillomavirus Reference Center. Officialy established HPV types: Available from: https://www.hpvcenter.se/human_reference_clones/. Accessed [October 2024].
- 57. McBride AA. Human papillomaviruses: diversity, infection and host interactions. Nature Reviews Microbiology. 2022;20(2):95-108.
- 58. de Villiers EM, Fauquet C, Broker TR, Bernard HU, zur Hausen H. Classification of papillomaviruses. Virology. 2004;324(1):17-27.
- 59. Al-Soneidar WA, Harper S, Madathil SA, Schlecht NF, Nicolau B. Do cutaneous human papillomavirus genotypes affect head and neck cancer? Evidence and bias-correction from a case-control study. Cancer Epidemiol. 2022;79:102205.
- 60. Laprise C, Madathil SA, Schlecht NF, Castonguay G, Soulières D, Nguyen-Tan PF, et al. Human papillomavirus genotypes and risk of head and neck cancers: Results from the HeNCe Life case-control study. Oral Oncol. 2017;69:56-61.
- 61. Bottalico D, Chen Z, Dunne A, Ostoloza J, McKinney S, Sun C, et al. The oral cavity contains abundant known and novel human papillomaviruses from the Betapapillomavirus and Gammapapillomavirus genera. J Infect Dis. 2011;204(5):787-92.
- 62. Agalliu I, Gapstur S, Chen Z, Wang T, Anderson RL, Teras L, et al. Associations of Oral α -, β -, and γ -Human Papillomavirus Types With Risk of Incident Head and Neck Cancer. JAMA Oncology. 2016;2(5):599-606.
- 63. Al-Soneidar WA, Harper S, Coutlée F, Gheit T, Tommasino M, Nicolau B. Prevalence of Alpha, Beta, and Gamma Human Papillomaviruses in Patients With Head and Neck Cancer and Noncancer Controls and Relation to Behavioral Factors. The Journal of Infectious Diseases. 2023;229(4):1088-96.
- 64. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011;29(32):4294-301.
- 65. Mehanna H, Beech T, Nicholson T, El-Hariry I, McConkey C, Paleri V, et al. Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer--systematic review and meta-analysis of trends by time and region. Head Neck. 2013;35(5):747-55.
- 66. Olshan AF. Epidemiology, pathogenesis, and prevention of head and neck cancer: Springer; 2010.
- 67. Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. The lancet oncology. 2010;11(8):781-9.
- 68. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, et al. Case—control study of human papillomavirus and oropharyngeal cancer. New England Journal of Medicine. 2007;356(19):1944-56.

- 69. D'Souza G, Agrawal Y, Halpern J, Bodison S, Gillison ML. Oral sexual behaviors associated with prevalent oral human papillomavirus infection. J Infect Dis. 2009;199(9):1263-9.
- 70. Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma. J Clin Oncol. 2015;33(29):3235-42.
- 71. Ndiaye C, Mena M, Alemany L, Arbyn M, Castellsague X, Laporte L, et al. HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis. Lancet Oncol. 2014;15(12):1319-31.
- 72. Mahuli AV, Sagar V, Kumar A, Mahuli SA, Kujur A. A Systematic Review and Meta-Analysis Assessing the Role of Oral Health as a Risk Factor in Oral Cancer. Cureus. 2023;15(5):e39786.
- 73. Li R, Hou M, Yu L, Luo W, Liu R, Wang H. Association between periodontal disease and oral squamous cell carcinoma: a systematic review and meta-analysis. Br J Oral Maxillofac Surg. 2023;61(6):394-402.
- 74. Hashim D, Sartori S, Brennan P, Curado MP, Wünsch-Filho V, Divaris K, et al. The role of oral hygiene in head and neck cancer: results from International Head and Neck Cancer Epidemiology (INHANCE) consortium. Ann Oncol. 2016;27(8):1619-25.
- 75. Deo PN, Deshmukh R. Oral microbiome and oral cancer The probable nexus. J Oral Maxillofac Pathol. 2020;24(2):361-7.
- 76. Perea-Milla Lopez E, Minarro-Del Moral R, Martinez-Garcia C, Zanetti R, Rosso S, Serrano S, et al. Lifestyles, environmental and phenotypic factors associated with lip cancer: a case—control study in southern Spain. British journal of cancer. 2003;88(11):1702-7.
- 77. Kenborg L, Jørgensen AD, Budtz-Jørgensen E, Knudsen LE, Hansen J. Occupational exposure to the sun and risk of skin and lip cancer among male wage earners in Denmark: a population-based case—control study. Cancer Causes & Control. 2010;21(8):1347-55.
- 78. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and cancers of the mouth, pharynx and larynx. Available from: https://www.wcrf.org/wp-content/uploads/2021/02/mouth-pharynx-larynx-cancer-report.pdf. Accessed [May 20, 2024].
- 79. Luo Z, Zhu X, Hu Y, Yan S, Chen L. Association between dietary inflammatory index and oral cancer risk: A systematic review and dose–response meta-analysis. Front Oncol. 2022;12.
- 80. Saraiya V, Bradshaw P, Meyer K, Gammon M, Slade G, Brennan P, et al. The association between diet quality and cancer incidence of the head and neck. Cancer Causes Control. 2020;31(2):193-202.
- 81. Chuang S-C, Jenab M, Heck JE, Bosetti C, Talamini R, Matsuo K, et al. Diet and the risk of head and neck cancer: a pooled analysis in the INHANCE consortium. Cancer Causes Control. 2012;23:69-88.
- 82. Miller A. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 38. Tobacco smoking: International Agency for Research on Cancer, Lyon, pp. 421. ISBN 92-832-1238-X. Food Chem Toxicol 25:627–628.1987.
- 83. Shrotriya S, Deep G, Gu M, Kaur M, Jain AK, Inturi S, et al. Generation of reactive oxygen species by grape seed extract causes irreparable DNA damage leading to G 2/M arrest and apoptosis selectively in head and neck squamous cell carcinoma cells. Carcinogenesis. 2012;33(4):848-58.
- 84. Prasad R, Katiyar SK. Bioactive phytochemical proanthocyanidins inhibit growth of head and neck squamous cell carcinoma cells by targeting multiple signaling molecules. 2012.

- 85. Chaturvedi AK. Epidemiology and clinical aspects of HPV in head and neck cancers. Head and neck pathology. 2012;6(1):16-24.
- 86. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nature reviews Disease primers. 2020;6(1):1-22.
- 87. The Oral Cancer Foundation. Oral Cancer Facts: Available from: https://oralcancerfoundation.org/facts/. Accessed [June 16, 2024].
- 88. Shanmugham JR, Zavras AI, Rosner BA, Giovannucci EL. Alcohol-folate interactions in the risk of oral cancer in women: a prospective cohort study. Cancer Epidemiol Biomarkers Prev. 2010;19(10):2516-24.
- 89. Government of Canada. Oral Cancer: Available from: https://www.canada.ca/en/public-health/services/oral-diseases-conditions/oral-cancer.html. Accessed [February 20, 2024].
- 90. Canadian Cancer Statistics Advisory Committee in collaboration with the Canadian Cancer Society and Statistics Canada and the Public Health Agency of Canada. *Canadian Cancer Statistics 2021*. Toronto, ON: Canadian Cancer Society; 2021. Available from: cancer.ca/Canadian-Cancer-Statistics-2021-EN. Accessed [October 12, 2023].
- 91. Negri E, Boffetta P, Berthiller J, Castellsague X, Curado MP, Dal Maso L, et al. Family history of cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Int J Cancer. 2009;124(2):394-401.
- 92. Shete S, Liu H, Wang J, Yu R, Sturgis EM, Li G, et al. A Genome-Wide Association Study Identifies Two Novel Susceptible Regions for Squamous Cell Carcinoma of the Head and Neck. Cancer Res. 2020;80(12):2451-60.
- 93. Conway DI, Petticrew M, Marlborough H, Berthiller J, Hashibe M, Macpherson LM. Socioeconomic inequalities and oral cancer risk: a systematic review and meta-analysis of case-control studies. Int J Cancer. 2008;122(12):2811-9.
- 94. Conway DI, Brenner DR, McMahon AD, Macpherson LM, Agudo A, Ahrens W, et al. Estimating and explaining the effect of education and income on head and neck cancer risk: INHANCE consortium pooled analysis of 31 case-control studies from 27 countries. Int J Cancer. 2015;136(5):1125-39.
- 95. ThekkePurakkal AS, Naimi AI, Madathil SA, Kumamangalam Puthiyannal SH, Netuveli G, Sacker A, et al. Differential impact of socioeconomic position across life on oral cancer risk in Kerala, India: An investigation of life-course models under a time-varying framework. Community Dent Oral Epidemiol. 2018;46(6):592-600.
- 96. Krishna Rao S, Mejia GC, Roberts-Thomson K, Logan RM, Kamath V, Kulkarni M, et al. Estimating the effect of childhood socioeconomic disadvantage on oral cancer in India using marginal structural models. Epidemiology. 2015;26(4):509-17.
- 97. Ju X, Canfell K, Smith M, Sethi S, Garvey G, Hedges J, et al. High-Risk Human Papillomavirus—Related Oropharyngeal Squamous Cell Carcinoma Among Non-Indigenous and Indigenous Populations: A Systematic Review. Otolaryngology—Head and Neck Surgery. 2021;165(1):23-32.
- 98. Mazereeuw MV, Withrow DR, Diane Nishri E, Tjepkema M, Marrett LD. Cancer incidence among First Nations adults in Canada: follow-up of the 1991 Census Mortality Cohort (1992-2009). Can J Public Health. 2018;109(5-6):700-9.
- 99. Sankaranarayanan R, Ramadas K, Amarasinghe H, Subramanian S, Johnson N. Oral Cancer: Prevention, Early Detection, and Treatment. In: Gelband H, Jha P, Sankaranarayanan R, Horton S, editors. Cancer: Disease Control Priorities, Third Edition (Volume 3). Washington (DC): The International Bank for Reconstruction and Development / The World Bank © 2015 International Bank for Reconstruction and Development / The World Bank.; 2015.

- 100. Withrow DR, Pole JD, Nishri ED, Tjepkema M, Marrett LD. Cancer Survival Disparities Between First Nation and Non-Aboriginal Adults in Canada: Follow-up of the 1991 Census Mortality Cohort. Cancer Epidemiol Biomarkers Prev. 2017;26(1):145-51.
- 101. Badri P, Ganatra S, Baracos V, Lai H, Amin M. Oral Cavity and Oropharyngeal Cancer Surveillance and Control in Alberta: A Scoping Review. J Can Dent Assoc 2021;87:14 March 8, 2021.
- 102. Valdez JA, Brennan MT. Impact of Oral Cancer on Quality of Life. Dental Clinics. 2018;62(1):143-54.
- 103. Talamini R, Bosetti C, La Vecchia C, Dal Maso L, Levi F, Bidoli E, et al. Combined effect of tobacco and alcohol on laryngeal cancer risk: a case-control study. Cancer Causes Control. 2002;13(10):957-64.
- 104. Collins S. Controversies in multimodality therapy for head and neck cancer: clinical and biologic perspectives. Comprehensive management of head and neck tumors. 1999.
- 105. Valdez JA, Brennan MT. Impact of Oral Cancer on Quality of Life. Dent Clin North Am. 2018;62(1):143-54.
- 106. Breeze J, Rennie A, Dawson D, Tipper J, Rehman KU, Grew N, et al. Patient-reported quality of life outcomes following treatment for oral cancer. Int J Oral Maxillofac Surg. 2018;47(3):296-301.
- 107. Stark DPH, House A. Anxiety in cancer patients. British journal of cancer. 2000;83(10):1261-7.
- 108. Pang J, Tringale KR, Tapia VJ, Moss WJ, May ME, Furnish T, et al. Chronic opioid use following surgery for oral cavity cancer. JAMA Otolaryngology–Head & Neck Surgery. 2017;143(12):1187-94.
- 109. Ko HC, Mehra MN, Burr AR, Wieland AM, Kimple RJ, Hartig GK, et al. Opioid use in patients undergoing treatment for oral cavity cancer. J Pain Manag. 2020;13(2):167-73.
- 110. McQueen N, Partington EJ, Harrington KF, Rosenthal EL, Carroll WR, Schmalbach CE. Smoking cessation and electronic cigarette use among head and neck cancer patients. Otolaryngology--Head and Neck Surgery. 2016;154(1):73-9.
- 111. Kung L-Y, Li T-I, Chung C-H, Lee S-P, Chen G-S, Chien W-C, et al. Risk of depression in patients with oral cancer: a nationwide cohort study in Taiwan. Scientific Reports. 2021;11(1):23524.
- 112. Kam D, Salib A, Gorgy G, Patel TD, Carniol ET, Eloy JA, et al. Incidence of Suicide in Patients With Head and Neck Cancer. JAMA Otolaryngol Head Neck Surg. 2015;141(12):1075-81.
- 113. Jacobson JJ, Epstein JB, Eichmiller FC, Gibson TB, Carls GS, Vogtmann E, et al. The cost burden of oral, oral pharyngeal, and salivary gland cancers in three groups: commercial insurance, Medicare, and Medicaid. Head Neck Oncol. 2012;4:15.
- 114. Garaszczuk R, Yong JHE, Sun Z, de Oliveira C. The Economic Burden of Cancer in Canada from a Societal Perspective. Current Oncology. 2022;29(4):2735-48.
- 115. Tucker-Seeley RD, Yabroff KR. Minimizing the "financial toxicity" associated with cancer care: advancing the research agenda. JNCI: Journal of the National Cancer Institute. 2016;108(5).
- 116. National Cancer Institute. Financial toxicity (financial distress) and cancer treatment (PDQ®)—Health professional version.: National Institutes of Health. Available from: https://www.cancer.gov/about-cancer/managing-care/track-care-costs/financial-toxicity-hp-pdq. Accessed [October 16, 2024].
- 117. Terrell JE, Nanavati K, Esclamado RM, Bradford CR, Wolf GT. Health impact of head and neck cancer. Otolaryngology—Head and Neck Surgery. 1999;120(6):852-9.
- 118. The Financial Hardship of Cancer in Canada: A Literature Review. Canadian Cancer Survivor Network: Available from. Accessed

- 119. Scully C. Challenges in predicting which oral mucosal potentially malignant disease will progress to neoplasia. Oral diseases. 2014;20(1):1-5.
- 120. Awan K. Oral Cancer: Early Detection is Crucial. J Int Oral Health. 2014;6(5):i-ii.
- 121. LeHew CW, Epstein JB, Kaste LM, Choi YK. Assessing oral cancer early detection: clarifying dentists' practices. J Public Health Dent. 2010;70(2):93-100.
- 122. Canadian Cancer Statistics Advisory Committee. *Canadian Cancer Statistics 2018*. Toronto, ON: Canadian Cancer Society; 2018. Available from: cancer.ca/Canadian-Cancer-Statistics-2018-EN.pdf. Accessed [January 10, 2024].
- 123. Stefanuto P, Doucet J-C, Robertson C. Delays in treatment of oral cancer: a review of the current literature. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2014;117(4):424-9.
- 124. Gigliotti J, Madathil S, Makhoul N. Delays in oral cavity cancer. International Journal of Oral and Maxillofacial Surgery. 2019;48(9):1131-7.
- 125. Peacock ZS, Pogrel MA, Schmidt BL. Exploring the reasons for delay in treatment of oral cancer. The Journal of the American Dental Association. 2008;139(10):1346-52.
- 126. Yu T, Wood RE, Tenenbaum HC, Perio D. Delay in Diagnosis of Head and Neck Cancers: University of Toronto; 2007.
- 127. Scott SE, Grunfeld EA, McGurk M. Patient's delay in oral cancer: A systematic review. Community dentistry and oral epidemiology. 2006;34(5):337-43.
- 128. Badri P, Baracos V, Ganatra S, Lai H, Samim F, Amin M. Retrospective study of factors associated with late detection of oral cancer in alberta: A qualitative study. PLOS ONE. 2022;17(4):e0266558.
- 129. Gómez I, Warnakulasuriya S, Varela-Centelles P, López-Jornet P, Suárez-Cunqueiro M, Diz-Dios P, et al. Is early diagnosis of oral cancer a feasible objective? Who is to blame for diagnostic delay? Oral Diseases. 2010;16(4):333-42.
- 130. Kassirian S, Dzioba A, Hamel S, Patel K, Sahovaler A, Palma D, et al. Delay in diagnosis of patients with head-and-neck cancer in Canada: impact of patient and provider delay. Current Oncology. 2020;27(5):467-77.
- 131. Mathur R, Singhavi HR, Malik A, Nair S, Chaturvedi P. Role of Poor Oral Hygiene in Causation of Oral Cancer—a Review of Literature. Indian Journal of Surgical Oncology. 2019;10(1):184-95.
- 132. Zhang Y, Fakhry C, D'Souza G. Projected Association of Human Papillomavirus Vaccination With Oropharynx Cancer Incidence in the US, 2020-2045. JAMA Oncology. 2021;7(10):e212907-e.
- 133. Government of Canada. Public Health Agency of Canada. Vaccination Coverage Goals and Vaccine Preventable Disease Reduction Targets by 2025: Available from: https://www.canada.ca/en/public-health/services/immunization-vaccine-priorities/national-immunization-strategy/vaccination-coverage-goals-vaccine-preventable-diseases-reduction-targets-2025.html. Accessed [June 2, 2022].
- 134. Gillison ML. Human papillomavirus-related diseases: oropharynx cancers and potential implications for adolescent HPV vaccination. Journal of Adolescent Health. 2008;43(4):S52-S60.
- 135. Government of Canada. Human papillomavirus (HPV) vaccines: Canadian Immunization Guide: Available from: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-9-human-papillomavirus-vaccine.html. Accessed [November 1, 2024].
- 136. Government of Canada. Updated recommendations on human papillomavirus vaccines: Available from: <a href="https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/national-advisory-committee-health/services/publications/vaccines-immunization/national-advisory-committee-health/services/publications/vaccines-immunization/national-advisory-committee-health/services/publications/vaccines-immunization/national-advisory-committee-health/services/publications/vaccines-immunization/national-advisory-committee-health/services/publications/vaccines-immunization/national-advisory-committee-health/services/publications/vaccines-immunization/national-advisory-committee-health/services/publications/vaccines-immunization/national-advisory-committee-health/services/publications/vaccines-immunization/national-advisory-committee-health/services/publications/vaccines-immunization/national-advisory-committee-health/services/publications/vaccines-immunization/national-advisory-committee-health/services/publications/vaccines-immunization/national-advisory-committee-health/services/publications/vaccines-immunization/national-advisory-committee-health/services/publications/vaccines-hea

- <u>immunization-updated-recommendations-hpv-vaccines.html#table1</u>. Accessed [November 1, 2024].
- 137. Steben M, Durand N, Guichon JR, Greenwald ZR, McFaul S, Blake J. A National Survey of Canadian Adults on HPV: knowledge, attitudes, and barriers to the HPV vaccine. Journal of Obstetrics and Gynaecology Canada. 2019;41(8):1125-33. e6.
- 138. Government of Canada. Canada's Tobacco Strategy: Available from: https://www.canada.ca/en/health-canada/services/publications/healthy-living/canada-tobacco-strategy.html. Accessed [February 20, 2024].
- 139. Government of Canada. Justice Laws Website. Non-Smokers' Health Act: Available from: https://laws-lois.justice.gc.ca/eng/acts/n-23.6/page-1.html. Accessed [February 20, 2024].
- 140. Government of Canada. Tobacco Products Appearance, Packaging and Labelling Regulations (TPAPLR) Available from: https://www.canada.ca/en/health-canada/services/smoking-tobacco/regulating-tobacco-vaping/tobacco/appearance-packaging-labelling.html. Accessed [February 2024].
- 141. Government of Canada. Justice Laws Website. Tobacco and Vaping Products Act, Part III Labelling: Available from: https://laws-lois.justice.gc.ca/eng/acts/t-11.5/page-3.html#docCont. Accessed [February 2024].
- 142. Government of Canada. Regulating tobacco and vaping products: Tobacco products regulations.: Available from: https://www.canada.ca/en/health-canada/services/smoking-tobacco/regulating-tobacco-vaping/tobacco.html. Accessed [February 2024].
- 143. Government of Canada. Justice Laws Website. Tobacco Repoting Regulations. Available at: https://laws-lois.justice.gc.ca/eng/regulations/SOR-2000-273/index.html. Accessed on February 2024.
- 144. Government of Canada. Justice Laws Website. Promotion of Tobacco Products and Accessories Regulations (Prohibited Terms): Available from: https://laws-lois.justice.gc.ca/eng/regulations/SOR-2011-178/FullText.html. Accessed [February 2024].
- 145. Government of Canada. Justice Laws Website. Tobacco (Access) Regulations: Available from: https://laws.justice.gc.ca/eng/regulations/SOR-99-93/FullText.html. Accessed [February 2024].
- 146. Government of Canada. Quitting smoking: Provincial and territorial services Available from: https://www.canada.ca/en/health-canada/services/smoking-tobacco/quit-smoking/provincial-territorial-services.html. Accessed [February 2024].
- 147. Canadian Partnership Against Cancer. Smoking Cessation in cancer care across Canada, 2022-23 Available from: https://www.partnershipagainstcancer.ca/topics/smoking-cessation-cancer-care-2022-2023/canada/. Accessed [April 2024].
- 148. Government of Canada. Adjusted Rates of Excise Duty on Tobacco Products Effective April 1, 2024: Available from: https://www.canada.ca/en/revenue-agency/services/forms-publications/publications/edn91/adjusted-rates-of-excise-duty-on-tobacco-products-effective-april-1-2024.html. Accessed [April 2024].
- 149. Stockwell T, Leng J, Sturge J. Alcohol pricing and public health in Canada: issues and opportunities. Centre for Addictions research of BC; 2006. Available from. Accessed 150. Giesbrecht N, Wettlaufer A, Thomas G, Stockwell T, Thompson K, April N, et al. Pricing of alcohol in C anada: A comparison of provincial policies and harm-reduction opportunities. Drug and alcohol review. 2016;35(3):289-97.
- 151. Canadian Partnership Against Cancer. Provincial/ Territorial Alcohol Policy Pack: Available from: https://www.partnershipagainstcancer.ca/wp-content/uploads/2018/05/provincial-territorial-alcohol-policy-pack-en.pdf. Accessed [April 2024].

- 152. Babor TF, Caetano R, Casswell S, Edwards G, Giesbrecht N, Graham K, et al. Alcohol: No Ordinary Commodity: Research and Public Policy: Oxford University Press; 2010 01 May 2010.
- 153. Callaghan RC, Sanches M, Gatley JM, Stockwell T. Impacts of drinking-age laws on mortality in Canada, 1980-2009. Drug Alcohol Depend. 2014;138:137-45.
- 154. Callaghan RC, Sanches M, Gatley JM, Stockwell T. Impacts of drinking-age laws on mortality in Canada, 1980–2009. Drug and Alcohol Dependence. 2014;138:137-45.
- 155. BC Cancer. Oral Cancer Prevention Program: Available from: http://www.bccancer.bc.ca/health-professionals/clinical-resources/oral. Accessed [June 2022].
- 156. Friesen R, McGaw T, Peters E, Lai H. A retrospective analysis of referral patterns to a university oral medicine clinic. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2019;128(4):381-5.
- 157. Melchior M, Chastang JF, Mackinnon D, Galera C, Fombonne E. The intergenerational transmission of tobacco smoking--the role of parents' long-term smoking trajectories. Drug Alcohol Depend. 2010;107(2-3):257-60.
- 158. Campbell JM, Oei TP. A cognitive model for the intergenerational transference of alcohol use behavior. Addict Behav. 2010;35(2):73-83.
- 159. Nilsson M, Stenlund H, Weinehall L, Bergstrom E, Janlert U. "I would do anything for my child, even quit tobacco": bonus effects from an intervention that targets adolescent tobacco use. Scand J Psychol. 2009;50(4):341-5.
- 160. Australian Government. National Tobacco Campaign: Available from: https://www.health.gov.au/our-work/national-tobacco-campaign?language=en. Accessed [July 2022].
- 161. C K, Vimala HS, J S. A systematic review of artificial intelligence techniques for oral cancer detection. Healthcare Analytics. 2024;5:100304.
- 162. Shawky E., M. A., F. R., S. B., Bashir T., M. E., Saber M. [2024]. Early Diagnosis of Oral Cancer Using Image Processing and Artificial Intelligence. Fusion: Practice and Applications. (): 293-308. DOI: https://doi.org/10.54216/FPA.140122.
- 163. Rokhshad R, Mohammad-Rahimi H, Price JB, Shoorgashti R, Abbasiparashkouh Z, Esmaeili M, et al. Artificial intelligence for classification and detection of oral mucosa lesions on photographs: a systematic review and meta-analysis. Clin Oral Investig. 2024;28(1):88.
- 164. Vollmer A, Hartmann S, Vollmer M, Shavlokhova V, Brands RC, Kübler A, et al. Multimodal artificial intelligence-based pathogenomics improves survival prediction in oral squamous cell carcinoma. Sci Rep. 2024;14(1):5687.