UNIVERSIDADE FERNANDO PESSOA

THE ROLE OF DIABETES MELLITUS IN ORAL CANCER: AN UMBRELLA REVIEW OF SR AND MA

[O papel da Diabetes Mellitus no cancro oral: uma revisão umbrella de RS e MA]

Dissertação de Mestrado

[Mestrado Integrado em Medicina Dentária]

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Orientadoras:

Mestre Alexandra Arcanjo

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“I know of no better life purpose than to perish in attempting the great and the impossible.”

- Friedrich Nietzsche

I dedicate this work to my
parents, to whom I owe
everything that I have and
that I am.

Thank you.

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ABSTRACT:

The purpose of this study was to assess if there is a positive association between Diabetes Mellitus (type 1, type 2 or gestational diabetes) with the development of head and neck cancer. An umbrella review was performed by conducting a systematic search in Cochrane, EBSCO, Wiley, ScienceDirect and PubMed, within the time frame from January 2000 until January 2024. The umbrella review was registered in PROSPERO (CRD42024512151). Both systematic reviews (SR) and meta-analysis (MA) of observational studies were included. Article selection (Preferred Reporting Items for Systematic Reviews and Meta-Analysis - PRISMA), quality assessment and risk of bias assessment (standard Joanna Briggs Institute Critical Appraisal Checklist) and the graphical representation of Overlap for OVErviews (GROOVE) tool to study double counting in different SR were performed by two independent reviewers (FF and AA) with a third one (MCM) consulted to solve discrepancies. Seven SR were included. Of the 20 associations of different kinds of head and neck cancers with all different types of diabetes, it was found that 9 of those (45%) have statistically significant positive correlation (using different association measures: OR, HR, RRR and RR). The most robust evidence was found for the relation with overall cancer ($RR_{\text{fixed effects}}$=1.22, 95%CI=1.16-1.29, $p<0.001$). For oral cancer, this significant increase was found with RRR=1.13 ($p=0.009$), with OR=1.32 ($p<0.001$), with HR=1.73 ($p<0.05$) and with RR=1.28 ($p<0.05$). For oropharyngeal, the significant increase was depicted with RR=1.18 ($p<0.05$) and with HR=1.53 ($p<0.05$). Regarding head and neck cancer, the significant increase was shown with HR=1.47 ($p<0.05$). For nasopharyngeal, it was found with OR=1.40 ($p<0.05$). Low heterogeneity was observed in two of the papers, nothing mentioned for one, and it was high in the remaining four. Risk factors were reported in five of the systematic reviews, but that was not the focus of the present umbrella. In conclusion, though Diabetes Mellitus has been extensively studied in relation to risk of developing cancer, the selected studies have not been done specifically regarding head and neck cancer. Although strong claims of significance exist for the overall types, in this case, still only a minority of the associations with oral cancer have robust supporting evidence without hints of bias. It is necessary to keep conducting studies on this matter, collecting data following the same structure and for all types of head and neck cancer.

Keywords: diabetes; cancer; carcinoma; tumor; malignant; oral; buccal; head; neck

RESUMO

O objetivo deste estudo foi avaliar se existe uma associação positiva entre a Diabetes Mellitus (tipo 1, tipo 2 ou diabetes gestacional) e o desenvolvimento de cancro da cabeça e pescoço. Foi efectuada uma revisão geral através de uma pesquisa sistemática nas bases de dados Cochrane, EBSCO, Wiley, ScienceDirect e PubMed, no período de janeiro de 2000 a janeiro de 2024. A revisão geral foi registada no PROSPERO (CRD42024512151). Foram incluídas tanto revisões sistemáticas (RS) como meta-análises (MA) de estudos observacionais. A seleção dos artigos (Preferred Reporting Items for Systematic Reviews and Meta-Analysis - PRISMA), a avaliação da qualidade e do risco de enviesamento (Joanna Briggs Institute Critical Appraisal Checklist) e a ferramenta graphical representation of Overlap for OVErviews (GROOVE) para estudar a dupla contagem em diferentes RS foram realizadas por dois revisores independentes (FF e AA), tendo um terceiro (MCM) sido consultado para resolver discrepâncias. Foram incluídas sete RS. Das 20 associações de diferentes tipos de cancros da cabeça e do pescoço com todos os diferentes tipos de diabetes, verificou-se que 9 delas (45%) têm uma correlação positiva estatisticamente significativa (utilizando diferentes medidas de associação: OR, HR, RRR e RR). A evidência mais robusta foi encontrada para a relação com o cancro geral ($RR_{efeitos\ fixos}$ =1,22, IC95%=1,16-1,29, p<0,001). Para o cancro oral, este aumento significativo foi encontrado com RRR=1,13 (p=0,009), com OR=1,32 (p<0,001), com HR=1,73 (p<0,05) e com RR=1,28 (p<0.05). Relativamente ao cancro da orofaringe, o aumento significativo foi registado com RR=1,18 (p<0,05) e com HR=1,53 (p<0,05). Relativamente ao cancro da cabeça e pescoço, o aumento significativo foi demonstrado com HR=1,47 (p<0,05). Para o cancro da nasofaringe, verificou-se um OR=1,40 (p<0,05). A heterogeneidade foi baixa em dois dos artigos, não foi mencionada em um, e foi alta nos quatro restantes. Os fatores de risco foram referidos em cinco das revisões sistemáticas, mas não foi esse o foco do presente estudo. Em conclusão, embora a Diabetes Mellitus tenha sido amplamente estudada em relação ao risco de desenvolver cancro, os estudos selecionados não foram feitos especificamente em relação ao cancro da cabeça e do pescoço. Embora existam fortes reivindicações de significância para os tipos gerais, neste caso, apenas uma minoria das associações com o cancro oral tem provas de apoio sólidas sem indícios de enviesamento. É necessário continuar a realizar estudos sobre este assunto, recolhendo dados seguindo a mesma estrutura e para todos os tipos de cancro da cabeça e do pescoço.

Palavras-chave: diabetes; cancro; carcinoma; tumor; maligno; oral; bucal; cabeça; pescoço

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Abbreviations, acronyms or symbols

AMSTAR - Assessing the Methodological Quality of Systematic Reviews

BMI - Body Mass Index

CKD - Chronic Kidney Disease

CVD - Cerebral Vascular Disease

DM2 - Diabetes Mellitus 2

DNA - Deoxyribonucleic Acid

EBV - Epstein-Barr virus

GDM - Gestacional Diabetes Mellitus

GRADE - Grading of Recommendations Assessment Development and Evaluation

GROOVE - Graphical Representation of Overlap for OVErviews

HF - Heart Failure

HIV - Human Immunodeficiency virus

HPV - Human Papillomavirus

HR -– Hazard Ratio

IGF - Insulin-like Growth Factors

IL-6 - Interleukin-6

JBI - Joanna Briggs Institute

MA - Meta Analysis

MOOSE - Meta-analyses Of Observational Studies in Epidemiology

NOS - Newcastle-Ottawa Quality Assessment Scale

OGT - Oral glucose tolerance test

OR - Odd Ratio

PECO –-Population, Exposure, Comparison, Outcome

PRISMA - Preferred Reporting Items for Systematic reviews and Meta-Analyses

RR - Relative Risk

RRR - Relative Risk Ratio

SPD - Sociedade Portuguesa de Diabetologia

SR - Systematic Review

TNM - Tumor, Node, Metastasis

UK - United Kingdom

WHO - World Health Organization

I. INTRODUCTION

Oral cancer is a serious disease that affects the oral cavity and its surrounding structures, such as the lips, tongue, jugal mucosa, palate and floor of the mouth. It can manifest itself in various ways, including persistent ulcers, abnormal white or red spots, swelling or unexpected volumes, persistent pain and difficulty in speaking, swallowing or chewing. It is more common in men aged 50 and over. The treatment of oral cancer depends on several factors, including the stage of the disease, the location of the tumor, the patient's general state of health and other individual factors. Generally, treatment involves a multidisciplinary approach that can include surgery, radiotherapy, chemotherapy and targeted therapies.

Diabetes is a chronic condition that affects the body's ability to regulate blood sugar levels. There are two main types of diabetes: type 1, which is an autoimmune condition in which the body does not produce insulin, and type 2 which is more common and occurs when the body does not use insulin effectively. Both types of diabetes can increase the risk of various health complications as well as conditioning the treatment of certain diseases.

The relationship between oral cancer and diabetes is complex and multifactorial. Some studies suggest that diabetic patients may have a slightly increased risk of developing oral cancer, possibly due to factors such as chronic inflammation and a compromised immune system. In addition, inadequate control of blood sugar levels in diabetic patients may contribute to the growth and spread of oral cancer.

The aim of this work was to examine and synthesize the evidence generated globally in systematic reviews and in meta-analysis on the link between a diabetic individual having a higher risk of developing oral cancer by exploring biological mechanisms, to consider and raise awareness of the clinical implications, and to provide useful guidelines for the prevention and management of this specific relationship.

The research methodology used was based on carrying out an independent search in Cochrane, EBSCO, Wiley, Science Direct and PubMed covering publications in the time frame beginning of 2019 and the end of 2023, subject to inclusion criteria, the use of only meta-analysis and systematic reviews of epidemiological studies investigating the

association between diabetes and oral cancer, and exclusion criteria such as unnamed languages (if they appear) and the time period of publication. The query was: "(((diabetes) AND (cancer OR carcinoma OR neoplasm OR tumor OR neoplasm OR malignant) AND (oral OR buccal OR head OR neck))) AND (meta-analysis OR systematic review) ". The search was launched in the abstract and title (PubMed) and in the abstract in the other databases. In PubMed, MeSH words such as "neoplasm", "tumor", "neoplasm" and "carcinoma" were used.

II. STATE OF THE ART

1. Oral cancer – GENERAL DESCRIPTION

i. FORMATION PROCESS

Head and neck carcinoma is the 6th most prevalent cancer in the world being roughly 2.8% of all kinds of cancers (Ordem dos Médicos Dentistas, [OMD]).

Oral squamous cell carcinoma is a malignant disease of genetically altered oral epithelial cells (keratinocytes) with the capacity of uncontrolled proliferation, increased survival, invasion of the underlying connective tissue through the basement membrane and destruction of local tissues. This malignant transformation occurs due to: interactions with environmental factors that abnormally activate some intracellular transduction pathways that trigger relevant transcription factors that regulate the expression of genes that mediate cell attachment, proliferation, differentiation, migration and apoptosis; to random genetic mutations; to intrinsic non-genetic factors (inflammation and changes in the mechanical properties of the extracellular matrix) (Feller et al., 2021).

Cancer cells exhibit very specific characteristics such as cellular/nuclear pleomorphism, increased nucleus/cytoplasm ratio, nuclear hyperchromatism, evident and multiple nucleoli, coarse chromatin, increased mitotic activity and atypical mitoses (Singh & Lele, 2022).

Most oral cancers develop from pre-cancerous oral epithelium with keratinocytes in different molecular stages of transformation by the proliferation of a genetically altered cell in the basal cell layer. There is also a histopathological classification called TNM (Tumur, Node, Metastasis) which resides in the degree of differentiation, growth pattern and depth of invasion and whether it is vascular/neural, bone involvement, number of lymph nodes involved and whether or not there is metastasis (Farah et al., 2019; National Cancer Institute, 2022).

The places most affected by this type of cancer are the tongue, the floor of the mouth, the gums and the alveolar mucosa, in descending order (Feller et al., 2021).

ii. SIGNS AND SYMPTOMS

Initially, patients do not feel pain, which appears progressively over time.

The common signs and symptoms can be the appearance of persistent ulcers, lesions or hard mass that do not heal that can be white, red or mixed lesions. The appearance of pain, paresthesia and possible loss of sensitivity, lymphadenopathy, tissue growth and persistent bad breath (Ordem dos Médicos Dentistas, [OMD]).

Diagnosis is made through screening consultations with physical exams and using complementary exams such as biopsies , clinical analyzes or radiological exams.When detected early, oral cancer has a cure rate of between 80 and 90% (Wang et al., 2023).

iii. COMMON RISK FACTORS AND PREVENTION STRATEGIES

Tobacco contains numerous carcinogenic chemicals such as tar and nicotine that can cause mutations in the deoxyribonucleic acid (DNA) of cells, making them susceptible to becoming malignant. Furthermore, tobacco smoke containing these substances, whether inhaled or chewed, in direct contact with the oral mucosa, can damage the lining of the mouth over time , which causes potentially cancerous lesions (Table 1) (Petti, S. 2009).

In addition to this, tobacco has the ability to inhibit natural defense mechanisms as well as weaken the immune system, making the body less capable of fighting cancer cells and even increasing the vulnerability of their mutation and transformation (Luo & Stent, 2024). Finally, this risk factor also has the particularity of influencing angiogenesis, the formation of new blood vessels from pre-existing ones, which benefits tumor growth, as it needs a blood supply to grow and spread (Saman, et al., 2020).

The association of tobacco with excessive alcohol consumption also increases the risk of oral cancer (Petti, S. 2009) (Table 1).

Excessive **alcohol** consumption causes chronic irritation of the oral mucosa as well as ethanol, the chemical substance in alcohol, is metabolized in the body into acetaldehyde - an extremely toxic and carcinogenic substance - by the enzyme alcoholic dehydrogenase, which , in both situations, increase the risk of genetic mutations and propensity for cancerous transformation. Wine is the alcoholic drink with the greatest impact compared to others. (Boccia, et al., 2009; Petti, 2009)

Like tobacco, alcohol also compromises the immune system as it is directly related to the absorption of essential nutrients, which weakens the body's ability to defend itself and eliminate abnormal cells in the cell cycle (Gateway Foundation).

Nutritional habits are essential to be monitored, for example, the deficiency in vitamin C can harm the body's ability to repair DNA damage, as seen in the table 1, a deficiency in antioxidants, which exist in fruits and vegetables, makes the body lose its ability to protect cells against oxidative damage (National Institutes of Health, 2020).

Still within nutritional factors, a diet rich in processed foods, sugar and saturated fats and low in fiber, may be associated with obesity, which is a risk factor for oral cancer. Excess salt causes chronic irritation of the mucous membranes and, consequently, increases the risk of cancer (Petti, 2009).

In the case of cancer patients undergoing aggressive treatments, poor nutrition can negatively affect both the response to treatment and their quality of life (National Cancer Institute, 2018).

Excessive exposure to the sun, particularly ultraviolet radiation, is a risk factor for cancer of the lip, specifically lower lip (Table 1), as the skin is thin and can cause damage over time and increase the risk of developing lip cancer. It is important to use lip sunscreen regularly (Van der Waal, 2010).

With **aging**, there is an accumulation of exposure to risk factors, genetic damage to cells and a weakening of the immune system, making it less effective in suppressing cancer (Berben et al., 2021).

The fact that **men have a higher risk** (Table 1) of developing oral cancer is due to the fact that they are more exposed to behavioral factors such as tobacco and alcohol, there are anatomical differences associated with certain types of cancer such as the larynx (men have an Adam's apple that can be more affected by smoking) and its greater sensitivity to the human papillomavirus (HPV) (Radoi et al., 2015).

The **biological risk** of oral cancer depends on the type of microorganism (Table 1):

- The oncogenic capacity of HPV infection, particularly the HPV-16 and HPV-18 types, transmitted through sexual contact, causes changes in the cells of the oral cavity and throat with the possibility of progressing to cancer, because it degrades the p53 protein (suppressor of tumors) (McCullough et al., 2010);

- Epstein-Barr Virus (EBV) is associated with infectious mononucleosis and when it becomes a chronic situation it can increase the risk of developing cancer (Patel, et al., 2022);

- Bacterial plaque microorganisms, such as *Phorphyromonas gingivalis*, *Fusobacterium nucleatum* and *Prevotella spp.*, cause chronic inflammation of the gums, periodontal disease and produce chemical substances that can damage the DNA of cells, making them more susceptible to carcinogenic mutations (Bhuyan, et al., 2022; Salazar-Flores, et al., 2022);

- Patients with human immunodeficiency virus (HIV) have a compromised immune system and, consequently, may be at greater risk of developing oral cancer (Chen et al., 2015).

The **genetic** part is also an indisputable risk factor, and individuals with first-degree relatives who have had cancer may have a slightly increased risk of developing it as well (Table 1). Furthermore, genetic predisposition is due to mutations in specific genes that affect the regulation of cell growth and DNA repair - CDKN2A - which, when exposed to environmental factors, such as tobacco and alcohol, increase the risk of developing oral cancer (Aghiorghiesei, et al., 2022).

There are also genetic polymorphisms and rare hereditary genetic syndromes that significantly increase the risk of developing this disease, such as Fanconi, Bloom and Peutz-Jeghers Syndrome, which present specific genetic mutations that predispose to the development of not only oral cancer but other types of cancer (Garutti, et al., 2023).

Professional exposure turns out to be a risk factor due to inhalation, ingestion, contact with the skin or mucous membranes or due to the accumulation of exposure over time to substances (Table 1) such as: ionizing radiation (health professionals who work with radiological examinations or radiotherapy) (Yoshinaga, et al., 2004), silica (mining, construction and foundry sector) mainly associated with lip cancer, asbestos (mining, shipbuilding and factories), industrial chemical agents (such as arsenic, nickel and formaldehyde) (Puñal-Riobóo, et al., 2010), toxic dust, fumes and pesticides (Salazar-Flores, et al., 2022).

Chronic lesions that do not heal or persistent inflammation can be a risk for oral cancer (Table 1):

- Chronic inflammation is associated with chronic tissue inflammation, the latter of which can damage cells, making them more susceptible to genetic mutations (Kay, et al., 2019);

- Damage to cells caused by physical irritations (such as prosthetics or biting the cheek), chemical (tobacco) or infectious irritations (Piemonte, et al., 2018);

- Prolonged infections such as long-lasting HPV infections (McCullough et al., 2010);

- Potentially malignant conditions, such as leukoplakia, erythroplakia, erythroleukoplakia, oral submucosal fibrosis, oral lichen planus and chronic hyperplastic candidiasis, which are oral lesions that present a greater risk of transforming into cancer (Mustafa et al., 2021);

Table 1

Risk factors and prevention measures for the presence of oral cancer.

	Description	Prevention
Tobacco	Tobacco, whether chewed or smoked, contains several carcinogenic substances that damage cells and increase the risk of oral cancer; Risk depends on the location of the cancer.	Smoking cessation; Implement measures regarding the sale and consumption of tobacco.
Alcohol	Excessive consumption increases the risk of developing oral carcinoma; When combined with tobacco, the risk is even greater.	Moderation in alcohol consumption; Implement measures regarding the sale and consumption of alcohol.
Microorganisms	HPV causes changes in the cells of the oral cavity and throat, such as the degradation of the p53 protein; EBV, which is associated with infectious mononucleosis and acts in tumor progression; Microorganisms in bacterial plaque can produce chemical substances that damage the DNA of oral cells, making them more susceptible to mutations; Patients with HIV have a compromised immune system.	HPV vaccination; Control of the microbiota of the oral cavity through periodic consultations with the dentist.
Nutricion	Vitamin C deficiency impairs DNA damage repair;	Work together with a nutritionist during treatment;

	Description	Prevention
	In the absence of antioxidants, cells lose protection against oxidative damage; Foods rich in sugar and fat are associated with obesity, a risk factor for oral cancer; Excess salt causes irritation of the mucous membranes; Poor nutrition negatively affects cancer treatment.	Advise a balanced/healthy diet.
Sun exposure	Very associated with lower lip cancer	Reduce sun exposure; Use of ip sunscreen regularly
Family history	First-degree relatives with this condition increase the risk of developing the disease; Genetic predisposition due to mutations in specific genes that affect the regulation of cell growth and DNA repair; Rare hereditary genetic syndromes; Genetic polymorphisms.	Understand and investigate the mechanisms of genetic changes that initiate the development of cancer; Cytogenetic control.
Age and gender	Risk increases with age, especially after age 45; More common in men than women.	Surveillance and implementation of screening programs.
Chronic injuries	Chronic inflammation; Damage to cells; Prolonged infections; Precancerous conditions; Exposure to additional risk factors.	Early detection and treatment; Adoption of a healthy lifestyle excluding the use of tobacco and alcohol consumption; Maintain good oral hygiene.
Professional exposure	Ionizing radiation; Silica (mainly on the lips); Asbestos; Industrial chemical agents such as arsenic, nickel and formaldehyde; Toxic dust and fumes.	Use of personal protective equipment; Training and respect for workplace safety standards; Constant surveillance and control of those exposed.
Health literacy	Poor literacy in oral health and oral cancer makes populations more vulnerable, especially to mortality, as they do not know how to identify the symptoms.	Health education.

iv. TYPES OF TREATMENT

Oral cancer treatment varies depending on the stage of the disease, location of the tumor, the patient's age, general health and other factors (National Health System [NHS], 2017). It usually involves the combination of several therapeutic approaches such as:

- **Surgery**: often the main treatment, depending on the location and stage of the cancer, may include removal of the tumor, margins of healthy tissue around it and, in advanced cases, removal of part of the jaw and/or tongue. Surgery is also used to reconstruct the site after tumor removal (Omura, 2014).

- **Radiotherapy**: can be used as curative, adjuvant, neoadjuvant or palliative treatment. Ionizing radiation energy in the form of X-rays, gamma rays, neutrons or protons is used and can be described in terms of dose, fractionation and sequencing. This radiation serves to destroy cancer cells. It can be used before surgery to reduce the size of the tumor, after surgery to eliminate any remaining cancer cells, or as the main treatment in certain cases of oral cancer. (Feller et al., 2021)

- **Chemotherapy**: involves medications that attack cancer cells throughout the body. It is often used in combination with radiotherapy for more advanced stages,after surgery but also as induction therapy (before surgery) (Omura, 2014).

- **Targeted therapy**: Some types of oral cancer respond to medications that target the activity of specific proteins involved in tumor growth (Cancer Research UK). A monoclonal antibody, estimated Glomerular Filtration Rate (EGFR), inhibitor such as cetuximab improves the survival rate (Omura, 2014).

- **Immunotherapy**: is an innovative approach that applies biotechnology and immunological methods aiming to strengthen the patient's immune system to fight cancer. Some treatments within immunotherapy, such as immune checkpoint inhibitors, are being investigated for oral cancer. It includes adoptive cell immunotherapy, antibody-based therapy, cytokine therapy, tumor vaccines therapy and gene therapy (Liu, et al., 2022).

- **Photodynamic therapy**: this treatment involves the administration of a photosensitive substance that is activated by a specific light source at a specific wavelength, releasing reactive oxygen species (ROS) with cytotoxic properties, which destroys cancer cells or inhibits their growth. It is used for cancers with a minimum of invasiveness with better clinical outcomes, having fewer complications than surgery or radiation therapy (Mosaddad, et al., 2023).

- **Intensity Modulated Radiotherapy** (IMRT): is an advanced form of radiotherapy that allows intensity-modulated beams to deliver radiation with multiple intensity levels for any single-beam direction and any single-source position to the tumor allowing dose gradients with narrower margins than with conventional methods, minimizing damage to surrounding healthy tissues (O'Sullivan et al., 2012).

- **Rehabilitation**: After treatment, rehabilitation is often necessary to help patients regain function and quality of life. This may include multiple professionals like maxillofacial surgeons, dentists, dental hygienists, physiatrists, speech pathologists and nurses (Matsuda, et al., 2022).

In maxillary rehabilitation, which has as its main objective the separation of the oral and nasal cavities, allowing the restoration of oral, respiratory function and facial aesthetics, one of the most used rehabilitations are obturator prostheses. There are different types, such as (Pace-Balzan et al., 2011):

- Surgical: immediate after surgery, support soft tissues and decrease scars; 1 to 4 weeks; give psychological benefit for patients.
- Interim: derives from surgical ones within 10 to 14 days and used for 3 to 6 months until the tissues are stabilized; it prepares the space for the definitive one.
- Definitive: it is dependent on compliance with prosthodontic principles and consistent with oncological ones also; it can be used together with implants improving prognosis.

The specific treatment plan for oral cancer is determined by the oncologist, oral and maxillofacial surgeon, and other team members based on a thorough assessment of the patient. Early detection is essential to increase the chances of successful treatment.

v. CONSEQUENCES OF TREATMENT

The consequences of any treatment vary from person to person depending on age, sex, ethnicity, general health status, body mass index, exposed organ, environmental variants, as well as the radiation dose, the form of administration, the extent and location of the area to be irradiated, likewise the quality and penetrating power of the radiation and the patient's individual factors. These can be temporary, which normally appear during treatment, and are mostly reversible, or they are late complications and commonly

irreversible (Table 2) – but all of them greatly reduce the quality of life of each patient who undergoes oral cancer treatments.

Table 2

Early and late effects of cancer treatment. (adapted de G. Feller et al., 2021)

Early effects	**Late effects**
Skin erythema	Fibrosis
Dry skin desquamation	Atrophy
Mucositis	Neural damage
Nausea and diarrhea	Second malignancies
Xerostomia	
Osteoradionecrosis	
Dysgeusia	Reduced organ functioning
Infections	Dysphagia
	Caries by radiation
	Trismus
	Soft tissue necrosis

Most patients with tumors in crucial organs such as the tongue, larynx, pharynx and upper esophageal sphincter, who undergo cancer treatment, experience **dysphagia** (difficulty swallowing) and **mucositis** due to neuromuscular conditions and as a result of weakness and irritation of the oral mucosa (Table 2), –,, and consequently, they have problems eating, whether in public or in their own homes, which also greatly affects their social life, leading to isolation. An esophagram demonstrated that, up to two years after surgery, **dysphagia** disappeared in 8% and its severity decreased in 32% of patients (Nguyen et al., 2006). On the other hand, **mucositis** occurs in around 80% of patients even during treatment, ending up disappearing spontaneously after one month of completion (Labbate & Denardim, 2003). **Mucositis** can be classified as grade 0, I, II, III or IV, according to the World Health Organization (WHO).

In the case of chemotherapy, it can cause systemic complications mainly in tissues with high mitotic activity such as the bone marrow, the gastrointestinal tract and the oral cavity. There is a homeostasis in the oral microbiota that can be completely unbalanced by chemotherapy sessions and the **mucositis** can be caused by it, developing systemic infections – the presence of unusual anaerobic bacteria in the oral cavity and an increase in the number of bacteria such as *Fusobacterium nucleatum, Porphyromonas gingivalis* and *Prevotella intermedia* wich are associated with **periodontal disease** and **oral candidosis** (Bruno et al. 2023).

Evaluating both chemotherapy and radiotherapy, one of the most common consequences is **xerostomia** (Table 2) – a sensation of dry mouth – that can be caused by hyposalivation, which, therefore, ends up triggering a series of other problems such as difficulty chewing, swallowing and even speaking, cavities and periodontal disease, atrophy and fissures in the soft tissues, a burning sensation in the tongue, there is a high tendency to infections due to the fact that, as there is less saliva, there is also a change in the pH of the environment and a decrease in immunoglobulins and, finally, causes very often halitosis. This condition can be classified as Grade I, II or III (Feio & Sapeta, 2005).

It is also important to mention another condition called **dysgeusia** (Table 2), that is changes in taste resulting from reduced salivary flow and biochemical changes in saliva (Rubira et al., 2007)

vi. INCIDENCE AND PREVALENCE

Head and neck cancers are coded in the International Classification of Oncological Diseases with the number C00-C14, if it is only of the oral cavity C00-06, salivary glands C07-08, oropharynx C09-10, nasopharynx C11, pharynx C14 and hypopharynx C12 -13 (World Health Organization, [WHO]).

In Portugal, according to the 2018 National Oncological Registry, oral cancer was the 11th most common type of cancer and is estimated to be around 3% of all diagnosed cancer cases, and in 2020 there were around 1103 new cases in both sexes with a large difference between men and women, 804 and 299, respectively (Global Health Observatory).

In the world, oral cancer, which includes lip, oral cavity and oropharynx, is one of the most common forms of cancer (6th place) with 377,713 cases and 177,757 deaths in 2020

, the incidence and prevalence vary considerably from one country to another , with high-risk areas, especially in regions where smoking and alcohol consumption are common. The HPV has played a fundamental role in increasing its incidence. The significantly most affected country is India with an incidence rate of 9.8 in 2020 (Hernández-Morales, et al., 2023).

The most common location is the floor of the mouth and 90% of the cancers found are carcinomas (Ordem dos Médicos Dentistas, [OMD]).

vii. POTENTIALLY MALIGNANT LESIONS

It is estimated that up to 35% of oral carcinomas arise from pre-existing potentially malignant lesions.

⇒ Leukoplakia – white lesion diagnosed by exclusion

Oral leukoplakia is a "white lesion or plaque, located on the oral mucosa, which cannot be classified as a known nosological entity" and is not removable by scraping (World Health Organization [WHO]). It may affect any part of the mouth but if the lesion is on the underside of the tongue, floor of mouth, or soft palate, then it is more likely to become precancerous (dysplastic) (Brigham and women's hospital [BWH]). Factors associated with these lesions are tobacco, alcohol, infection with *Candida Albicans*, EBV, HPV and HIV.

The prevalence is around 0.5 to 3.4% , the rate of malignancy is up to 33% in 10 years (the most common potentially malignant lesion present in 4.11% of the world population) and the most affected individuals are older men (Petti, 2003; Bagan, et al., 2010).

There are 2 clinical forms: **homogeneous leukoplakia**, an asymptomatic white plaque with an invariable texture throughout its entire length, and **non-homogeneous leukoplakia**, a white plaque associated with irregular texture. This second can be further divided into 3 subtypes: erythroleukoplakia, with both white and red color and which may or may not have associated symptoms; warty leukoplakia, with papillary and pointed projections and variable keratin thickness; nodular leukoplakia, presenting rounded polypoid protuberances. Apart from these, there is another specific form that is not considered a potentially malignant lesion: hairy leukoplakia (Seo, et al., 2010).

Proliferative verrucous leukoplakia is represented by focal, when early, or multiple heterogeneous and verruciform lesions over a wide area of the mucosa, with a high recurrence rate when removed (50%). It is more prevalent in older women and exhibits an aggressive and resistant biological behavior, progressing to squamous cell carcinoma (Thompson et al., 2021).

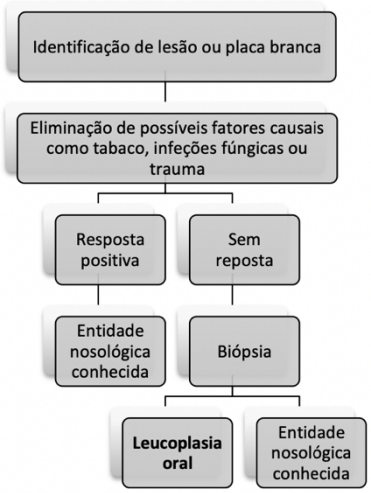
Homogeneous lesions typically present simple orthokeratosis, hyperkeratosis with different degrees of dysplasia, acanthosis and a poor subepithelial inflammatory infiltrate. In the case of non-homogeneous cases, we can already visualize epithelial hyperplasia with exophytic and/or endophytic growth as well as evident hyperkeratosis or hyperparakeratosis (Seo, et al., 2010).

Differential diagnosis: leukoedema, linea alba, squamous or warty carcinoma, oral lichen planus, white spongy nerve, lichenoid reactions, chronic hyperplastic candidiasis and *morsicatio bucarum* (Calatayud et al., 2009; van der Waal, 2009).

In case of leukoplakia, a biopsy is performed if there is presence of symptoms and also, if the lesion does not disappear after 4 weeks of the removal of the etiological factor. The definitive diagnosis is made by exclusion, eliminating other pathological changes that could be at the origin of the lesion and histopathological examination (van der Waal, 2010).

Figure 1

Diagnose of oral leucoplasia, adapted from Brouns e colaboradores 2013)



⇒ Erythroplakia

It is defined as a "red plaque lesion that cannot be clinically or pathologically characterized as any other definable disease" by the WHO. Unknown etiology, most associated with tobacco (Hosni et al, 2009). They represent 2% of all potentially malignant lesions (Sousa, 2011) and are more common in men over 40 years of age (van der Waal, 2009), with the most affected site being the soft palate. It has the greatest potential for malignant evolution (Hosni et al, 2009).

Clinically, they are asymptomatic, flat, atrophic and erosive lesions with a smooth or granular surface or in the form of depressions. Without keratin, red in color and with poorly defined and irregular edges. Most commonly solitary (van der Waal, 2009).

Histologically they exhibit mild or moderate epithelial dysplasia (9%), carcinoma *in situ* (40%) or microinvasive carcinoma (51%) (Reichart & Philipsen, 2005).

Differential diagnosis: erythematous candidiasis, atrophic or erosive lichen planus, pemphigoid, pemphigus, desquamative gingivitis and denture stomatitis (Reichart & Philipsen, 2005; van der Waal, 2009).

In this condition, a biopsy is always performed (Reichart & Philipsen, 2005).

⇒ Erythroleukoplakia

Clinically, it presents white and red areas with a flat or nodular surface with exophytic growths (van der Waal, 2009).

Histologically they exhibit hyperkeratosis or irregular hyperparakeratosis, dense inflammatory infiltrate, epithelial atrophy and advanced epithelial dysplasia in the red areas (Hosni et al, 2009).

Strongly associated with tobacco use, alcohol consumption and areca nut. It corresponds to 16% of potentially malignant lesions, is more common in individuals over 50 years of age and in the soft and hard palate area and has a 55% of progression to malignancy (Hosni et al, 2009).

⇒ Submucosal oral fibrosis

Chronic and progressive change in mucosal collagen metabolism either increases its quantity or degrades it.The main risk factor associated with this disease is the frequency and duration of chewing betel nut. Additionally, the malignancy rate is around 5% (Contreras et al., 2023).

The clinical condition proceeds in 3 phases, stomatitis, fibrosis and sequelae. In the first phase there are erythematous areas with vesicles that later rupture and produce painful ulcers that, when healing, give place to fibrosis. In a final phase, the fibrosis extends, hardens the mucosa and this gives rise to the consequences of the disease (Alshadwi & Bhatia, 2012) – difficulty in speaking, swallowing and chewing due to limitation of mouth opening, tongue rigidity and fibrous bands (Contreras et al., 2023).

Histologically, a large number of fibroblasts, fibrosis and dysplasia may also be observed. At different phases, epithelial modifications can correspond to atrophy with hypoplasia or hyperplasia and/or dysplasia. A shift in epithelial compliance happens because of the increased connective tissue fibrosis which favors the initiation of carcinomatous processes (Shih. et al., 2019).

Differential diagnosis: oral lichen planus, oral manifestation of scleroderma, generalized fibromatosis, iron deficiency anemia and amyloidosis (Contreras et al., 2023).

⇒ Oral lichen planus

Chronic mucocutaneous disease, inflammatory in nature and with an autoimmune component. It may also involve other areas, in addition to the oral cavity, such as the genital mucosa, nails and scalp (Al-Hashimi et al., 2007).

There is an abnormal immune response, mediated by cellular immunity, and it is thought that T lymphocytes are involved in a process that results in the apoptosis of cells when they infiltrate below the oral epithelium (Ismail et al, 2007).

The highest incidence occurs in females between the 3th and 6th decade, its prevalence is 0.5% to 2.6% and its malignancy rate is only close to 2% (Al-Hashimi et al., 2007). The most affected locations are the buccal mucosa, dorsal surface, lateral edges of the tongue and gums (Ismail et al, 2007).

Clinically, the lesions are multiple, symmetrical and bilateral, divided into 6 types: **reticular**, the most common and which displays a network of white Wickham striae or isolated white papules; **papular**; **plaque-like**; **erosive** with atrophic and erythematous areas due to inflammation with varying degrees of ulceration and surrounded by radiating white keratotic streaks; **atrophic**; **bullous**. Generally, oral lichen planus is asymptomatic, except in the case of the erosive and atrophic type, which may present with a sensation of pain and burning. All of these types can coexist, with phases of exacerbation but also of remission of the disease (Contreras et al., 2023).

Differential diagnosis: plaque type is confused with leukoplakia, the erosive and atrophic forms are similar to carcinoma and can also resemble pemphigus or pemphigoid. It can also be confused with lupus erythematosus lesions, oral lichenoid drug reactions, chronic ulcerative stomatitis or oral lichenoid contact hypersensitivity reactions (Contreras et al., 2023).

⇒ Chronic hyperplastic candidiasis

Candidiasis in general is caused by the fungus *Candida Albicans*. There are several subtypes of candidiasis, the most common being **pseudomembranous** candidiasis, but there are also the **atrophic/erythematous** form and the **chronic hyperplastic** form or also known as candida leukoplakia - the rarest form within the subtypes of candidiasis, having a higher incidence in men and the most common location is the buccal mucosa, especially at the corners of the lips (Huber & Terézhalmy, 2011).

Clinically, a demarcated, chronic, palpable and elevated painless lesion is observed, which may contain smaller white and translucent areas or completely opaque and extensive hard and rough ones (Jin, Keung & Samaranayake, 2009) . An important factor in the differential diagnosis of this condition is that these white plaques that form in the lesions cannot be removed by scraping, only excised - without pain or bleeding (Huber & Terézhalmy, 2011).

This disease is closely related to systemic factors such as hypoplasia, radiotherapy, immunosuppression such as in diabetes mellitus, the use of antibiotics, as well as local factors, including the use of an ill-fitting prosthesis (Shibata et al., 2011).

Regarding the capacity and probability of malignancy, it is relatively low, not exceeding 15% (Huber & Terézhalmy, 2011). There are cases of carcinomas that developed from these lesions, but we have not yet been able to find a cause-effect conclusion in the literature (Shibata et al., 2011).

Differential diagnosis: leukoplakia and erythroleukoplakia (Shibata et al., 2011).

viii. ORAL CANCER STAGE CLASSIFICATION

Cancer is generally divided according to the TNM Classification into two classifications: clinical (TNM or cTNM), as seen in Table 3, established before any therapy has been applied and obtained through clinical evaluation, imaging tests and biopsy, and

pathological (pTNM), from the analysis of the surgical specimen, after surgery. pTNM is applied for the purpose of obtaining a prognosis and guiding adjuvant therapy.

Table 3

Primary tumor classification (TNM) for oral cavity cancer, 8th edition (Adapted from AJCC Manual, 2018)

Primary Tumor (T)	**Regional Lymph Nodes (N)**	**Distant metastases (M)**
TX - Primary tumor cannot be evaluated.	NX - Non-evaluable regional lymph nodes.	Mx - Distant metastases cannot be assessed.
TO - No evidence of primary tumor	NO - No evidence of lymph node metastasis.	MO - No evidence of distant metastasis.
Tis - *in situ* carcinoma	-	-
T1 - Tumor ≤ 2 cm and depth of invasion (not thickness) <5 mm	N1 - Single ipsilateral lymph node metastasis >3 cm and absence of capsular leakage.	M1-Distant metastasis.
T2 - Tumor ≤ 2 cm, depth of invasion > 5 mm; or tumor >2 and ≤ 4 cm and depth of invasion ≤ 10 mm.	N2a – Single ipsilateral lymph node metastasis > 3 cm in greatest dimension, but <6 cm and without capsular leakage; or single ipsilateral or contralateral lymph node metastasis ≤3cm and absence of capsular leakage. N2b - Multiple lymph node metastases, ipsilateral, ≤6 cm and without capsular leakage. N2c - Bilateral or contralateral lymph node metastasis, ≤6 cm and absence of capsular leakage.	
T3 – Tumor > 2 and ≤ 4 cm with depth of invasion > 10 mm; or tumor > 4 cm with depth of invasion ≤ 10 mm	N3a - Lymph node metastasis > 6 cm in greatest dimension and absence of capsular leakage. N3b - Metastases in a single ipsilateral lymph node >3cm and ENE(+), or multiple metastases ipsilateral, contralateral, or bilateral with any capsular leakage.	
T4a – Moderately advanced local disease. Lip: invasion of cortical bone, alveolar nerve, floor of the mouth or facial skin. Oral cavity: invasion of adjacent structures only.		
T4b – Very advanced local disease.		

Primary Tumor (T)	Regional Lymph Nodes (N)	Distant metastases (M)
Invasion of the masticatory space, pterygoid plates, skull base or involvement of the internal carotid artery.		

2. ORAL CANCER - LOCATIONS

i. TONGUE

⇒ Histological description

Squamous cell carcinoma, accounting for 95% of cases, when referred to the base of the tongue, or oropharynx, has a typical expression - keratin deposits and nests of squamous cells with stromal fibrosis, cellular pleomorphism, typical mitosis and muscular invasion can be observed (Rivera et al., 2014; Gonzalez & Riera, 2020).

It is categorized into histological grades that reflect the degree of differentiation of the tumor cells – the less differentiated the tumor, the greater the aggressiveness and the worse the prognosis. Also the depth of invasion is the most important histologic component to determine the prognosis, type of treatment and risk of locoregional metastasis (Gonzalez & Riera, 2020).

⇒ Clinical description

In case of cancer on the anterior 2/3 of the tongue, symptoms may not initially be visible or painful. Tongue pain, non-healing ulcer (within 15 days) that causes pain and numbness when swallowing, and changes in the ability to form words are red flags. Other symptoms would be constant pain in the throat and so dysphagia plus weight loss, bad breath, the formation of a lump or causeless bleeding, which is characteristic of malignancy (Arrangoiz et al., 2018).

On the other hand, the characteristic symptoms of oropharyngeal cancer are odynophagia with associated otalgia (impairment of the glossopharyngeal and vagus nerve) and trismus due to interference with the pterygoid. Tongue protrusion is affected, therefore, both

swallowing and phonation are altered. Hypoglossal nerve involvement brings ipsilateral tongue deviation, lingual nerve involvement affects the sensations and the inferior alveolar nerve expresses as numbness. Unilateral nasal obstruction, hearing loss or otalgia means extension beyond the oral cavity (Gonzalez & Riera, 2020).

⇒ Treatment

It always depends on the stage of the disease and its characteristics. Surgical treatment is very aggressive but is the primary option (Arrangoiz et al., 2018).

T1 or T2 can be treated with only one modality, that is to say surgery or radiation. T3 or T4 need a multi-modality treatment with surgery and chemotherapy posteriorly - large tumors are removed through a partial glossectomy which may need locoregional flaps. The prognosis for this type of cancer is not obvious, as it has a high risk of developing metastases in the neck – the most common cause of death in these patients (Gonzalez & Riera, 2020).

⇒ Prevalence

- Age

Although tongue cancer is more common in adults and in individuals over the age of 45, the risk of incidence in young adults is increasing due to HPV infection (Paderno, et al., 2018) .

- Sex

Three times more common in men than in women, which is closely linked to the fact that they consume more tobacco and alcohol, although it has been increasing in young women which is believed to be associated with HPV (Gonzalez & Riera, 2020; Arrangoiz et al., 2018).

- Region

The most common area is in the anterior 2/3 of the lateral border, but it can also occur in the posterior 1/3 or base of the tongue, and this location is already considered the oropharynx (Arrangoiz et al., 2018).

- Ethnicity

It is an uncommon cancer with a higher incidence rate in Asia. Ethnicity itself has no influence, but the habit of smoking and particularly chewing betel nut, which is more present in certain populations, does (Arrangoiz et al., 2018).

- Risk factors

Smoking cigarettes and chewing tobacco increases the likelihood of this type of cancer by 10 times, according to the National Cancer Institute. Insufficient oral hygiene, elixirs with high percentage of alcohol, viral and fungal infections and HPV also contribute (Arrangoiz et al., 2018).

ii. FLOOR OF THE MOUTH

1) Histological description

There are several histological types of oral cancer associated with the floor of the mouth, the most prevalent being, at 95%, well-differentiated squamous cell carcinoma.

Typical presentation with muscle disorganization and invasion by neoplastic epithelial cells and inflammatory infiltrate (Rivera & Venegas, 2014).

2) Clinical description

It appears as an ulcerated lesion, with raised and hardened margins, close to the lingual frenum with a granular appearance on the base surface, grayish red and painless, which leads to the patient only consult the dentist when the tumor has grown to the neck (Cedars Sinai, 2020).

Other possible symptoms may include pain, sores that will not heal, loose teeth, difficulty swallowing, weight loss or ear pain (Middlesex Health, 2023).

3) Prevalence

- Age

Individuals over 40 years of age and the risk of developing this disease is directly proportional with increasing age(Rivera & Venegas, 2014).

- Sex

Greater association with males, three to four times more, since they are more exposed to the risk factors (Cedars Sinai, 2020).

- Region

The most common area for the development of floor of the mouth cancer is the anterior oral mucosa that extends under the tongue due to the high concentration of salivary glands in this region (World Health Organization [WHO]).

- Ethnicity

Insignificant.

- Risk factors

Tobacco, alcohol, HPV and immunosuppressors (Middlesex Health, 2023).

4) Treatment

Small superficial lesions by local excision; small lesions that invade adjacent tissues without reaching the lymph nodes with radiation; while larger lesions with palpable nodes require combined irradiation, chemotherapy and preoperative surgery (Middlesex Health, 2023).

iii. LIPS

⇒ Histological description

Squamous cell carcinoma is the most common (90%) and can progress to invasive cell carcinoma with possible metastasis in advanced stages only. Afterwards, the second type is basal cell carcinoma (less than 10%), which is less invasive and has a slower growing but way more common in the upper lip in opposition to the squamous one (Maruccia et al., 2012).

⇒ Clinical description

In the initial stage, it can be seen a papule or a plate which usually progresses into a vegetative or ulcerative form, also white or red lip patches, ulcers, lumps, or thickening,

an irritated area around the injury and/or neck lymphadenopathy. These symptoms can appear isolated or together (Alhabbab & Johar, 2022; Maruccia et al., 2012).

Self-examination is essential in the early diagnosis of this condition and increases the survival and cure rate up to 80% (Tsai, 2023).

⇒ Prevalence

- Age

Individuals between the 6th and 7th decade because of the accumulation of molecular changes after exposure to risk factors or due to the aging process (DNA damage) (Maruccia et al., 2012).

- Sex

Men have a higher incidence rate of lip cancer than women (WHO), due to their exposure to the sun in their jobs and also the tobacco and alcohol consumption. Also women protect themselves more often with the use of lipstick (Alhabbab & Johar, 2022).

- Region

This type of cancer is more prevalent in the lower lip, which is more exposed to direct ultraviolet rays with up to 85-95% (Alhabbab & Johar, 2022).

- Ethnicity

Black individuals have a lower incidence rate of lip cancer than caucasians due to the fact that they have more melanin - skin pigmentation (Maruccia et al., 2012).

- Risk factors

Exposure to ultraviolet radiation and its accumulation is the main risk factor associated with this type of cancer, especially in the lower lip, although tobacco and alcohol are also considered (Maruccia et al., 2012).

⇒ Treatment

There are two methods of action: surgery to remove the affected tissue along with some adjacent healthy tissue to ensure that all cancer cells are eliminated – better known as Mohs surgery, a successful technique for basal cell and squamous cell carcinomas (according to Skin Cancer Foundation) - or resort to radiotherapy and later the primary goal is to reconstruct the lip, depending on the depth and location of the defect, giving it full function and aesthetic (Alhabbab & Johar, 2022).

iv. PALATE

⇒ Histological description

It is more aggressive than in other locations. Hard palate tumors are diagnosed in more initial phases then the soft palate ones. Squamous cell carcinoma describes 50% of all hard palate cancers, with conventional well-differentiated tumor, papillary and verrucous forms, and 70% in the soft palate, the moderate, poor differentiated or the basaloid and acantholytic forms (Patru et al., 2020).

⇒ Clinical description

In the hard palate: typically it is seen painless ulcerating lesions that later on become painful but also it is possible to see a palatal mass, halitosis, dysphagia, odynophagia, bleeding, ill-fitting dentures or loose teeth (Young & Okuyemi, 2023) with , most of the times, extension to other anatomic regions such as maxillary sinus and skull base (Patru et al.,. 2020).

In the soft palate: initially as asymptomatic leukoplakia and after hypernasal speech, dysphagia, trismus, referred otalgia and/or hemoptysis (Patru et al., 2020).

⇒ Prevalence

- Age

More common in people with ages between 60 and 70 years old when regarding the hard palate and 60 years old if soft palate (Patru, N. 2020).

- Sex

Male predominance (Young & Okuyemi, 2023).

- Region

The lesion most commonly appears on the hard palate (Patru et al., 2020).

- Ethnicity

Very typical in India and Philippines (Patru et al., 2020).

- Risk factors

Tobacco, alcohol, bad hygiene, ill-fitting dentures and HPV infection (Young & Okuyemi, 2023).

⇒ Treatment

Most are treated with radiotherapy but there is a high rate of metastasis in the lymph nodes, therefore, this type of treatment may not be sufficient and it can be done together with removal surgery (Amar et al., 2004).

v. BUCCAL MUCOSA

⇒ Histological description

The main type of cancer in this area is squamous cell carcinoma with the majority being moderately differentiated (Huang et al. 2007).

Poor understanding of the extent of soft-tissue involvement in this area. Perineural invasion is an established predictor of poor prognosis in squamous cell carcinoma (Bobdey et al., 2018).

⇒ Clinical description

A sore in the mouth that does not heal, pain in the mouth, a lump or thickening on the cheek, a white or red patch on the gums or lining of the mouth, trouble chewing or

swallowing, numbness of an area of the mouth, loose teeth or pain around them (American Cancer Society [ACS], 2021).

⇒ Prevalence

- Age

As in the general description of oral cancer, it is more common in individuals over 40 years of age (Bobdey et al., 2018).

- Sex

There's a higher prevalence in males because they are more exposed to risk factors such as tobacco and alcohol (Bobdey et al., 2018).

- Region

It can occur in various areas of the jugal mucosa, but the most common region is the inner part of the cheek (Memorial Sloan Kettering Cancer Center, 2020).

- Ethnicity

It is the most common cancer in India (Bobdey, et al., 2018).

- Risk factors

Tobacco and alcohol in the United States and betel quid chewing in Asia (Huang et al. 2007).

⇒ Treatment

The main approach in the treatment of cancer of the jugal mucosa is surgery to remove the tumor along with part of the surrounding tissue, often used in early stages, and in some cases it is essential to subsequently perform reconstructive surgery to restore the function and appearance of the cheek. It can be also used radiotherapy and chemotherapy, the treatment modality depends of the primary carcinoma extension and a number of important clinical indices (Bobdey et al., 2018)

3. DIABETES MELLITUS

i. GENERAL DESCRIPTION

⇒ Prevalence

This condition is estimated to affect more than 400 million people worldwide. The most common form of this condition is Type 2 Diabetes, which is strongly associated with behavioral risk factors (World Health Organization [WHO]).

According to the Portuguese Society of Diabetology (SPD), in 2018 the prevalence of diabetes in Portugal was 13.6% (more than 1 million Portuguese people have this condition), with 5.9% of those still undiagnosed in 2017.

The Diabetes incidence rate gives us the identification of the number of new cases of Diabetes in the base population per year and there was a slight continuous increase in new cases in Portugal in the last 12 years, specifically between the years 2016 to 2018 (Table 4) (Portuguese Society of Diabetology [SPD]).

In general, there are more men than women with this disease and there is a higher prevalence in children from birth to 14 years old, in the case of type 1 diabetes, and in obese adults, in the case of type 2, with a strong increase in prevalence being noticeable with age (Portuguese Society of Diabetology [SPD]).

Table 4

Incidence of Diabetes in Portugal, adapted from Portuguese Society of Diabetology

Diabetes Incidence in Portugal

	2000	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	% aagr 2009-2018
Number of new cases per 100 000 individuals	377.4	571.1	623.5	651.8	500.9	557.1	522.1	591.5	**524.5**	**556.4**	**695.2**	**0.6%**
Total number of new estimated cases	38 988	60 385	65 921	68 715	52 531	58 090	54 167	61 169	**54 072**	**57 261**	**62 197**	**594 508**

⇒ Symptoms

Diabetes symptoms can vary according to the type of disease (1, 2 or gestational) and the stage of development. The most common are: **polydipsia** (excessive thirst due to the high amount of glucose in the blood); **polyuria** (hyperglycemia causes increased urine production); **polyphagia** (excessive hunger, constant feeling of hunger); **unintentional weight loss**, characteristic of type 1 or **unintentional weight gain** (obesity) associated with type 2 diabetes; **fatigue and weakness**; **blurred vision** (temporary); **recurrent infections** (the main ones are of the skin and urinary system); **slow healing** of wounds; **tingling and numbness in the extremities** (caused by diabetic neuropathy); **xerostomia** (feeling of dry mouth, due to polydipsia and polyuria); **mood changes**; **fruit-smelling breath** (in severe cases, the breath has a sweet smell) and **ketonuria** (ketones detected in urine), both only present in type 1 diabetes (American Diabetes Association [ADA], 2020).

Not all people with diabetes have all of these symptoms, but rather a set of them. Type 2 of this condition can be easier to miss because the symptoms develop slowly, highlighting the importance of regular early diagnostic exams (Diabetes UK, 2017).

⇒ Classification

The previously used classification followed the 1985 WHO rules and was based on the type of treatment of the disease, that is, it was divided into Diabetes Mellitus, Gestational Diabetes Mellitus and Intermediate Hyperglycemia..

Nowadays, the American Diabetes Association [ADA], 2010 classification is universally used, which is based on the etiology of the disease: Type 1 Diabetes, Type 2 Diabetes and Gestational Diabetes.

⇒ Oral consequences

The main consequences of this disease in the oral cavity are hyposalivation (caused both by hyperglycemia and medications), greater vulnerability to bacterial and fungal infections, delayed healing, tooth decay associated with poor diet and poor glycemic control and consequent premature loss of teeth. More symptoms may occur, such as dysphagia, burning mouth syndrome (BMS), alveolar bone resorption, gingivitis, oral

lichen planus, halitosis with ketonic odor (derived from the use of peripheral fat as a source of energy with the production of fatty acids that are transformed into ketone bodies), salivary gland dysfunction, trigeminal neuropathy and periodontal disease (bidirectional relation with prevalence and risk up to 3 times greater) (Alqadi, 2024).

⇒ Risk factors and prevention (Table 5)

Obesity/overweight due to excess body fat, especially around the abdominal region, can lead to insulin resistance (Ismail et al., 2021).

Lack of physical activity, as this helps improve insulin sensitivity (Ismail et al., 2021).

A diet rich in sugar, saturated fats and excess calories, as well as fast food, contributes to a greater risk of developing diabetes (World Health Organization [WHO]).

Heredity, as having first-degree relatives with this condition increases the risk of also developing it – genetic predisposition plays a fundamental role. On the other hand, there are also genes associated with this disease, such as some subtypes of HLA – human leukocyte antigen (Primavera et al., 2020).

Specific or combined childhood infections can cause type 1 diabetes by destroying pancreatic beta cells and, among viruses, the enteroviruses are the most commonly studied (Primavera et al., 2020).

The risk of developing diabetes increases with age – people over 45 have a higher risk (Ismail et al., 2021).

Some ethnic groups such as Hispanics, Native Americans, Africans and Asians are more predisposed to this disease than white people (Ismail et al., 2021).

Presence of factors associated with metabolic syndrome such as high blood pressure, high triglyceride levels and low (High-density Lipoprotein) HDL cholesterol levels (Ismail et al., 2021).

A history of gestational diabetes increases the risk of developing type 2 diabetes later in life and predisposes the child to also develop this condition (Plows et al., 2018).

There are studies that demonstrate the association between Polycystic Ovary Syndrome (PCOS) and the increased risk of developing diabetes because it affects the woman's hormonal system (Plows et al., 2018).

Smoking and excessive alcohol consumption are also part of this panoply of risk factors, which also complicate blood glucose control in diabetic individuals (Ismail et al., 2021).

There are also risk factors such as rapid growth of the baby, older maternal age and short duration of breastfeeding (Plows et al., 2018).

Table 5

Risk factors and measures of prevention in Diabetes Mellitus

Risk factor	**Prevention**
Obesity and overweight	Combine good nutritional and physical activity habits.
Lack of physical activity	Regular physical activity and reduce sedentary time.
Bad eating habits	Balanced diet rich in vegetables, fruits and lean proteins, avoiding sugars and saturated fats; control portion sizes.
Heredity	Know your family history.
Aging	Maintain glucose control.
African-American, Hispanic, Native American, and Asian ethnicity	
Metabolic syndrome	
History of gestational diabetes	Intensive blood glucose control.
Polycystic ovary syndrome	
Tobacco and alcohol	Stop consuming both.

⇒ Glucose values (Direção Geral da Saúde [DGS])

Fasting glucose testing is the most common test for diagnosing diabetes. It involves measuring blood glucose levels after a period of overnight fasting. The criteria are:

- Normal – value less than 100mg/dL or 5.6mmol/L;
- Pre-diabetes – value between 100 mg/dL or 5.6 mmol/L and 125mg/dL or 6.9 mmol/L;
- Diabetes – value equal to or greater than 126mg/dL or 7mmol/L in two measurements.

Oral glucose tolerance test (OGT) which consists of ingesting 75g of glucose orally after an overnight fast followed by repeated measurements of blood glucose levels at 2 hour intervals and the criteria includes:

- Normal – value less than 140mg/dL or 7.8mmol/L;
- Pre-diabetes – value between 140mg/dL or 7.8mmol/L and 199mg/dL or 11mmol/L;
- Diabetes – value equal to or greater than 200mg/dL or 11.1 mmol/L.

In case of **diagnosing gestational diabetes**, this measurement is made based on different values:

Fasting blood glucose, measurement taken at the first pregnancy consultation, with values between 92 mg/dl and 126 mg/dl (or ≥ 5.1 and < 7.0 mmol/l);

If fasting blood glucose is lower than 92 mg/dl, OGT is performed at 24-28 weeks of pregnancy. Gestational diabetes is considered with glucose values such as:

- In that moment, greater than 92 mg/dl (5.1 mmol/l);
- After 1 hour, greater than 180 mg/dl (10.0 mmol/l);
- After 2 hours, greater than 153 mg/dl (8.5 mmol/l).

Hemoglobin A1c test (measurement of average blood glucose levels over at least 3 months), with the following criteria:

- Normal – A1c less than 5.7%;
- Pre-diabetes – A1c between 5.7% and 6.4%;
- Diabetes – A1c equal to or greater than 6.5%.

A **random glucose test with classic symptoms** such as excessive thirst, frequent urination and unexplained weight loss, with a result equal to or greater than 200 mg/dL or 11 mmol/L in a blood sample may be indicative of diabetes.

ii. THE DIFFERENT TYPES OF DIABETES MELLITUS

⇒ Type 1

- Clinical description

Insulin-dependent type diabetes that results from the irreversible and variable autoimmune destruction, in some people faster and in others slower, of the β cells of the pancreas, which are responsible for the production of insulin which, in turn, regulates the amount of glucose in the blood and allows cells to generate energy. When there is a lack of insulin due to lack of production by β cells, there is also an increase in glucose present in the bloodstream (hyperglycemia), requiring external insulin (Diabetes Care, 2011).

It can be classified into subtypes 1A, autoimmune, which represents 70 to 90% of all type 1 diabetes, and subtype 1B, idiopathic (Atkinson et al., 2014).

- Stages (Diabetes Care*,* 2020)

Stage 1 is characterized by the existence of autoantibodies with completely normalized glucose levels – normoglycemia – in the blood and zero symptoms – "asymptomatic phase".

In **stage 2,** the positivity of 2 or more autoantibodies is observed, with changes in glucose metabolism – dysglycemia – but still without any symptoms.

Stage 3 is when the clinical manifestations of the disease itself appear, such as recent-onset hyperglycemia.

The duration and risk of progression of each phase are not yet fully understood.

- Symptoms

Of those mentioned above that are common to all types, the most specific to type 1 diabetes are the existence of unintentional weight loss, due to the burning of fat and muscle to obtain energy when glucose is not used properly, as well as fruit-smelling breath (due to the presence of ketones in the blood) and ketonuria (National Health System [NHS].

- Prevalence

Diabetes mellitus can appear in 5 to 10% of individuals. It is most commonly diagnosed in children, adolescents and young adults, with a higher incidence in males (Diabetes Care, 2011).

There may be a seasonal synchronization associated with diabetes autoimmunity that appears in the months or years before the onset of symptoms (Atkinson et al., 2014).

- Treatment (adapted from Erika F. Brutsaert in *Manual MSD*, 2022)

Treatment involves careful and regular administration of insulin, regular monitoring of blood glucose levels, control of diet and physical exercise.

In conventional treatment, multiple daily injections can be given with 2 types of subcutaneous insulin: either rapid or short-acting insulin administered by an insulin pump. Intensive treatment is used (monitoring glucose ≥ 4 times a day and insulin injection ≥ 3 times a day) or continuous administration of insulin, which is more effective than the conventional treatment.

Most patients with Diabetes Mellitus 1 can start treatment with a total dose of 0.2 to 0.8 units/kg/day of insulin – 40 to 60% as intermediate action and the remainder as rapid action to compensate for postprandial increases.

Types of insulin:

- **Fast action** - they are quickly absorbed because the inversion of amino acid pairs prevents the association of the insulin molecule with dimers or polymers. They generally start to reduce blood glucose within 15 minutes, but they have a short duration of action (< 4 hours). These insulins are most useful during meals to control postprandial plasma glucose spikes.
- **Regular action** - slightly slower onset of action (30 to 60 minutes) but longer duration (6 to 8 hours). It is the only form of insulin approved for IV use.
- **Intermediate action** - isophane insulin and regular U-500 with onset of action 2 hours after injection, maximum effect 4 to 12 hours after injection and duration of action 18 to 26 hours. Regular concentrated insulin U-500 can be administered 2 to 3 times a day.

- **Prolonged action** - Administered once a day, taking 3 days to reach a steady state and the dosage is less rigid.

- Complications

Poor glycemic control can change people's quality of life, as hyperglycemia can interfere and cause various complications, including acute myocardial infarction, chronic respiratory failure, neuronal damage, limb amputation, blindness or even a stroke (Rak & Bronkowska, 2019).

⇒ Type 2

- Clinical description

It can also be called “non-insulin dependent diabetes” or “adult-onset diabetes”. Type 2 is a complex metabolic disease that develops from the interaction between the individual genetic predisposition and environmental stimuli/exposures. It is characterized by hyperglycemia caused by failure of pancreatic β-cell islets resulting from the body's resistance to insulin. Islet insufficiency is associated with a decrease in β-cell mass and function and an increase in glucagon secretion. Therefore, there is a deficiency in the use of insulin, but it exists and is produced, which is why in type 2 diabetes there is no need for external insulin injections (Leahy, 2005).

- Symptoms

Hyperglycemia develops slowly over the years. These patients are at greater risk of developing macro and microvascular problems. This form of Diabetes is associated with **obese individuals** – insulin resistance can improve with weight reduction and pharmacological treatment of hyperglycemia (Diabetes Care, 2011).

- Prevalence

90 to 95% of diagnosed cases of diabetes mellitus type 2 are more common in women with previous Gestational Diabetes Mellitus and in individuals with high blood pressure or dyslipidemia (Diabetes Care, 2011).

- Treatment

Pharmacological treatment:

According to the SPD, with the last review in March 2020, it is necessary to determine the predominant associated pathologies in order to define the therapeutic scheme – Chronic kidney disease (CKD), Cerebral vascular disease (CVD), Heart Failure (HF) or without any associated pathology.

If there is **no associated pathology**: Metformin, SGLT-2 Inhibitors, GLP-1 Receptor Adonists, DPP-4 Inhibitors, Thiazolidinediones, Sulfonylureas, Basal Insulin, Rapid Insulin and Insulin Premix can be used.

If the individual suffers from **CKD**: the first association is with SGLT-2 Inhibitors and the second with GLP-1 Receptor Agonists, all others can be used with the exception of Sulfonylureas which should be avoided and all types of Insulin must be well titled because there is slower excretion by the kidneys.

The presence of **HF** tells us that: the 1st association is with SGLT-2 Inhibitors, the 2nd with GLP-1 Receptor Agonists and the 3rd with DPP-4 Inhibitors, all others can also be used with the exception of Thiazolidinediones, which are contraindicated.

When the patient suffers from **CVD,** then: the first association is with GLP-1 Receptor Agonists and the second with SGLT-2 Inhibitors as well as Thiazolidinediones. Also,Saxagliptin (DPP-4 inhibitor) must be avoided.

Non-pharmacological treatment:

Changing unhealthy habits, modifying diets including decreasing the amount of glycaemic index, bariatric surgery and physical exercise activate protective cellular mechanisms, improving mitochondrial function and insulin effectiveness (Raveendran, 2018).

- Complications

Chronic hyperglycemia in these cases is associated with microvascular complications such as nephropathy, neuropathy and peripheral retinopathy but can also generate earlier coronary, peripheral and cerebrovascular artery disease (Sahin & Birgili et al., 2019).

⇒ Gestational Diabetes

- Clinical description

It is diagnosed as glucose intolerance that results in hyperglycemia of varying intensity. This condition develops when the pancreas does not secrete enough insulin to keep up with the metabolic stress of pregnancy. The definition only applies if the condition did not persist after pregnancy. It most frequently occurs in the second half of pregnancy, from the 24th week onwards (Tavares et al., 2019).

- Symptoms

Gestational diabetes, in most cases, is not associated with any symptoms, and the diagnosis is made through laboratory analysis. However, it may be suspected during a fetal ultrasound (large fetus for the time of gestation) or present signs such as increased appetite, weight gain (in the pregnant woman or in the baby), dry mouth, nausea, increased urge to urinate, blurred vision, very thirsty and frequent urinary infections (Mompo et al., 2018).

- Prevalence

Gestational Diabetes Mellitus (GDM) is one of the most common complications of pregnancy today, occurring in 5% of all pregnant women. High-risk women with diabetes at their first prenatal visit should receive a diagnosis of non-gestational diabetes (according to the International Association of Diabetes and Pregnancy Study Groups). About 200,000 cases of GDM are detected annually and around 7% of pregnancies present more risks and complications due to this disease (Diabetes Care, 2011).

The risk and prevalence rate are much higher in some ethnic groups such as women of Mexican, American Indian, Asian and Pacific Islander descent.

- Treatment (adapted from Lara A. Friel, 2023, Manual MSD)

Intense and rigorous monitoring and control of blood glucose, physical activity and the diet itself to avoid weight gain of more than 6.8–11.3 kg.

Weekly examination starting in the 32nd week until delivery: cardiotocography, biophysical profiles and fetal movement counts.

The use of insulin, always with an individualized plan, is only for persistent hyperglycemia (fasting plasma glucose > 95 mg/dL or 2-hour postprandial > 120 mg/dL), after trying to diet for more than 2 weeks:

  - Obese patients - short-acting insulin before each meal.
  - Non-obese patients – 2/3 of the total dose in the morning and the remaining 1/3 in the afternoon; or use of long-acting insulin once or twice a day and insulin aspart immediately before breakfast, lunch and dinner.

- Complications

In the fetus: the association of this condition with a high risk of perinatal morbidity and mortality is elevated. The main complications are macrosomia/large fetuses that lead to birth trauma and shoulder dystocia (Tavares et al., 2019) but, on the other hand, premature birth (due to excess amniotic fluid), neonatal hypoglycemia, diabetes, obesity, hypocalcemia, risk of respiratory discomfort and hyperbilirubinemia (jaundice) can also occur (Massa et al., 2015).

In pregnant women: complications include maternal morbidity due to cesarean section and pre-eclampsia, the appearance of Diabetes Mellitus 2 (DM2) after birth, cardiovascular diseases such as high blood pressure and risk of repetition of GDM in the future (Mompo et al., 2018).

III. MATERIALS AND METHODS

This study was prepared in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines. The central question - Is there a relationship between diabetes mellitus and head and neck carcinoma? - was devised based on the PECO strategy (P=Population, E=Exposure, C=Comparison, O=Outcome) which can be seen in table 6.

This umbrella review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD 42024512151.

Table 6

Explanation of the PECO.

Population	Any kind of patients
Exposure	Having diabetes
Comparison	Not having diabetes
Outcome	Probability of people (with diabetes) having oral cancer

1. LITERATURE SEARCH

A search was carried out independently by two reviewers (FF and AA), with a third reviewer consulted at a given selection stage (MCM). The search was done per database according to the query explained in table 7, and all searches made from the beginning of 2000 to 15 January 2024, subject to the inclusion and exclusion criteria shown in table 8. The search on Science Direct was performed with fewer keywords because the platform only allowed the use up to 8 Boolean expressions.

Table 7

Query applied per database.

Database	**Query**
Cochrane	"((diabetes) AND (cancer OR carcinoma OR neoplasm OR tumor OR neoplasm OR malignant) AND (meta-analysis OR systematic review) AND (oral OR buccal OR head OR neck))" 2000-2023

Database	Query
EBSCO	"((diabetes) AND (cancer OR carcinoma OR neoplasm OR tumour OR neoplasm OR malignant) AND (meta-analysis OR systematic review) AND (oral OR buccal OR head OR neck))" 2000-2023
Science Direct	"((diabetes) AND (cancer OR carcinoma OR neoplasm) AND (meta-analysis OR systematic review) AND (oral OR head))" 2000-2023
PubMed	(("diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields] OR "diabets"[All Fields]) AND ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields] OR ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields] OR "carcinomas"[All Fields] OR "carcinoma s"[All Fields]) OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "neoplasia"[All Fields] OR "neoplasias"[All Fields]) OR ("cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor s"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields] OR "tumour s"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumors"[All Fields]) OR ("neoplasm s"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "neoplasm"[All Fields]) OR ("maligna"[All Fields] OR "malignas"[All Fields]) OR ("adenocarcinoma"[MeSH Terms] OR "adenocarcinoma"[All Fields] OR "adenocarcinomas"[All Fields] OR "adenocarcinoma s"[All Fields])) AND ("meta analysis"[Publication Type] OR "meta analysis as topic"[MeSH Terms] OR "meta analysis"[All Fields] OR ("systematic review"[Publication Type] OR "systematic reviews as topic"[MeSH Terms] OR "systematic review"[All Fields])) AND ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields] OR ("buccal"[All Fields] OR "buccally"[All Fields]) OR ("head"[MeSH Terms] OR "head"[All Fields]) OR ("neck"[MeSH Terms] OR "neck"[All Fields]))) AND ((meta-analysis[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (humans[Filter]) AND (english[Filter]) AND (2000:2023[pdat]))
Wiley	"((diabetes) AND (cancer OR carcinoma OR neoplasm OR tumour OR neoplasm OR malignant) AND (meta-analysis OR systematic review) AND (oral OR buccal OR head OR neck)) 2000-2023 and open access only

2. Selection of Studies and Eligibility

Duplicate articles were removed, and the reviewers screened the articles through the title and abstract and discussed the results based on the inclusion/exclusion criteria (cf. Table 8).

Table 8

Eligible criteria.

Inclusion criteria	Exclusion criteria
- Meta-analyses and systematic reviews - From the beginning of 2000 to the end of January 2024 - In English only - Open access (in the case of Science Direct) - Human participants, regardless of age and gender - Study subjects must have type 1 or type 2 diabetes	- Associations other than diabetes mellitus with oral cancer; - Other types of cancer as the outcome; - Studies with no original data or effect statistic reported. Results that cannot be interpreted/converted into categorical; - Human studies only, no in vivo animal or in vitro cell line studies.

3. Data Extraction

From the final articles that met the eligibility criteria and were included in this Umbrella Review, the following information was extracted for correct data analysis: a) author and year of publication, b) journal; c) population; d) outcome; e) sample size (number of patients and studies); f) guidelines used; g) PROSPERO code; h) search strategy and date; h) eligibility criteria; i) diagnostic criteria for diabetes or oral cancer conditions; j) assessment of the risk of bias; k) whether there was a meta-analysis or not; l) associated risk factors; m) conflict of interest; n) type of association; o) fixed or random RR or RR; p) fixed or random p value and prediction interval; q) Egger's P value; r) I2 and P value; s) AMSTAR and classification of the evidence of the articles.

4. Risk of Bias

The selected systematic reviews were critically appraised independently by two reviewers (FF and AA), and when necessary, a third reviewer (MCM) solved disagreements by consensus. We used the standard Joanna Briggs Institute Critical Appraisal Checklist for Systematic Reviews and Research Synthesis and followed the JBI Reviewers' Manual (2021) with 10 questions: 1) Is the review question clearly and explicitly stated? 2) Were the inclusion criteria appropriate for the review question? 3) Was the search strategy appropriate? 4) Were the sources and resources used to search for studies adequate? 5) Were the criteria for appraising studies appropriate? 6) Was critical appraisal conducted by two or more reviewers independently? 7) Were the methods used to combine studies appropriate? 8) Was the likelihood of publication bias assessed? 9) Were recommendations for policy and/or practice supported by the reported data? 10) Were the

specific directives for new research appropriate? Whenever necessary, authors of the systematic reviews will be contacted to request missing or additional information. For the checklist appraisal, studies that score low quality (≤3 yes/10 questions) were excluded, while include them when they show moderate quality (4-6 yes/10 questions) and high quality (7-10 yes/10 questions) (Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis. JBI, 2020) (cf. Table 13).

5. STRATEGY FOR DATA SYNTHESIS

The PRISMA flowchart was used to report the screening process. The key characteristics of all included studies were tabulated, accompanied by a narrative synthesis in text of the body of evidence. Findings on our review question were narratively presented, identifying the review that addresses it (number and reference) and supported by tables (main "summary of evidence").

Study double counting in different systematic reviews were presented visually using the Graphical Representation of Overlap for OVErviews (GROOVE) tool, which is a methodological approach and a tool that facilitates the assessment of overlap of primary studies among multiple systematic reviews. It has four sheets:

- The first sheet is an introductory sheet. It explains briefly what GROOVE is, how to use the tool and the optional advanced usage considering structural missingness.
- The second sheet is the only one that the user directly manipulates when entering data. It provides an empty matrix of evidence, supporting up to 70 systematic reviews and 1000 unique primary studies. The user must fill the systematic reviews IDs in the columns and the primary studies IDs in the rows.
- The third sheet is the GROOVE itself. It automatically provides the results of the overlap assessment, both overall and by pair of systematic reviews. It provides the results highlighting in colour the degree of overlap, according to previous recommendations (CCA 0-5% = slight; CCA 5-10% = moderate; CCA 10-15% = high; CCA>15% = very high)
- The fourth sheet is identical to the third, but it provides the results in greyscale colors.

IV. RESULTS

1. STUDY SELECTION

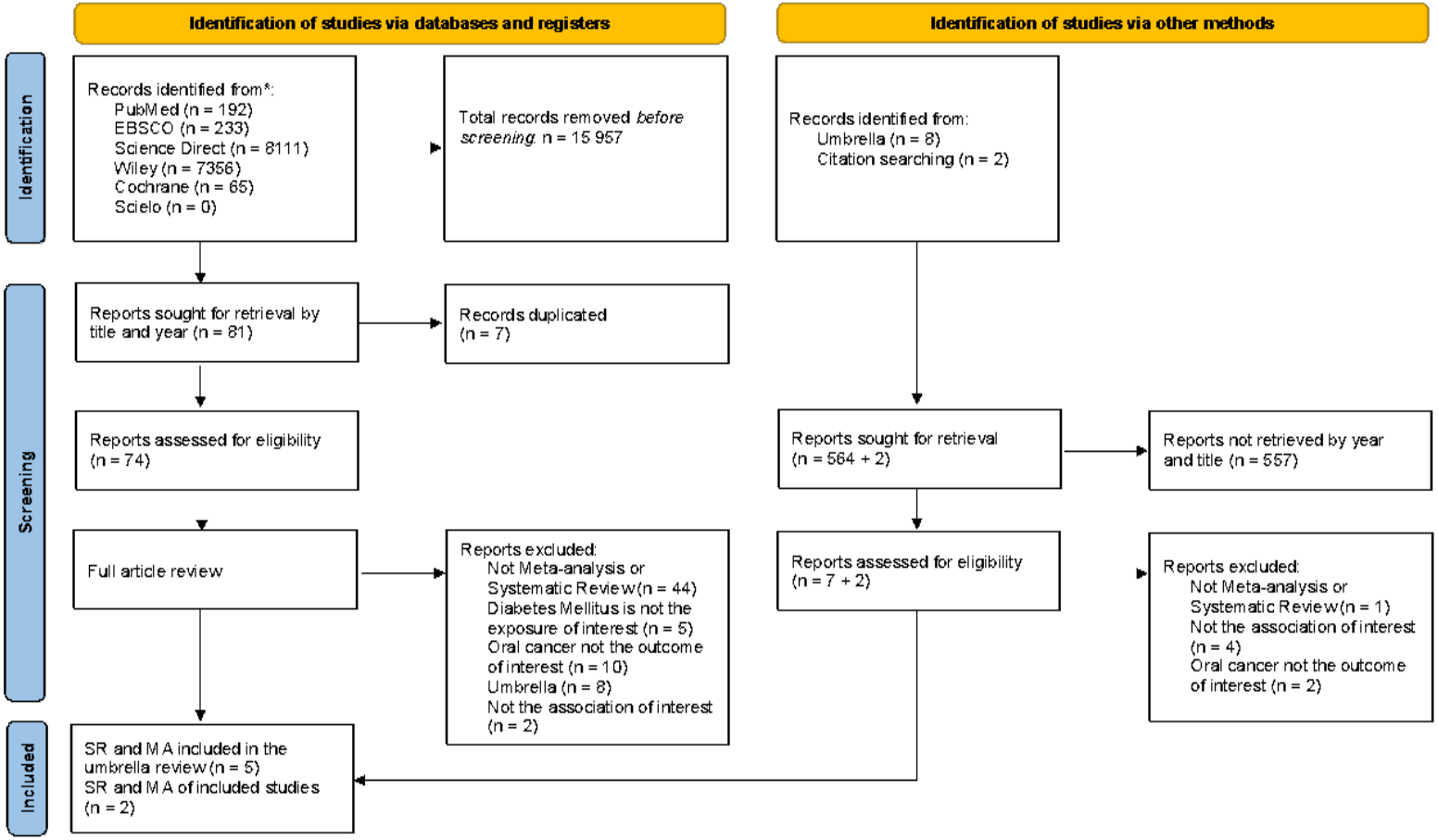
The search using all six databases and the query (keywords) mentioned in table 8 gave 15,957 articles, as can be seen in figure 2. In an initial phase 15876 were removed (after analyzing the title and year) remaining 81 studies, and from those 7 were removed due to duplication. The remaining 74 papers were screened and fully read by two authors (FF and AA) and later also approved by a third reviewer (MCM). The reading permitted the exclusion of a total of 69 papers, 44 because they were neither meta-analyses nor systematic reviews, 5 because Diabetes Mellitus was not the exposure of interest, 8 because they were Umbrella reviews, two because the association in question was not the one intended and 10 because oral cancer (any location of oral cancer) was not the outcome of interest. At the end this analysis gave five SR or MA papers to be included.

Apart from that, 566 articles were also identified that came from searching only for the words "Diabetes Mellitus and Oral Cancer" or taken out from the reference list of umbrellas that appeared in the previous search (564 belonging to eight umbrellas and two at random). Of these, 557 were excluded after analyzing the year of publication and title due to disagreement with the proposed objectives. After an evaluation by the two reviewers (FF and AA), three were excluded because they did not include the association under the scope of this study, one because oral cancer was not the outcome observed and one because it was not in the format of a systematic review or meta-analysis.

From the two search strategies, the literature search on this topic resulted in seven papers to be integrated in this umbrella review (cf. Figure 2).

Figure 2

PRISMA flowchart for the identification of the studies to be included in the umbrella review



2. STUDY CHARACTERISTICS

Of the seven systematic reviews and meta-analysis included in this umbrella review (cf. Table 9), there were associations of Diabetes Mellitus with risk of oral cancer overall (n = 7), oral cavity (n = 2), lip cancer (n = 1), head and neck (n = 3), nasopharynx (n = 2), orophanryngeal (n = 4), oral squamous cell carcinoma (n = 1) and mix between oral squamous cell carcinoma and oropharyngeal (n = 1). Although there was no restriction on the type of diabetes, there were two papers that focused just on Diabetes Mellitus type 2, one on Diabetes Mellitus type 1 and the five remaining others focused on both types of Diabetes Mellitus, not even making a distinction between types.

The number of studies overall was 350. We only considered the measures of association OR, RR, HR or RRR, and excluded data on incidence or mortality rates. The lowest number of cases of oral cancer in a meta-analysis was 6465 in Gong et al. (2015).

The risk of bias was evaluated with funnel plots and Begg's and Egger's tests in 4 of the 7 articles, the Joanna Briggs Institute was used in 2 and ROBINS-E in the last one (cf. Table 10).

There was only one systematic review that mentioned diagnostic criteria of *diabetes mellitus* for inclusion in the study (Gormley, et al. (2022). The range of years goes from 1965 to 2022 (cf. Table 10).

The studies recruited patients from 29 countries, 47 studies conducted in Asia, 73 in Europe, 29 in America, 6 in Oceania and 1 in Africa (cf. Table 11).

When it comes to the guidelines for selection of studies, it was quite equivalent with 5 of the 7 studies using the PRISMA method, 1 the MOOSE and the other have not got any. As well as it was also used the Newcastle-Ottawa Quality Assessment Scale (NOS) in 4 of them and GRADE in just 1 (cf. Table 12).

All of them were Meta-analyses and only three had a PROSPERO code (Ramos-Garcia, 2020; Dos Santos et al., 2022 and Gormley et al., 2022) (cf. Table 9).

There was no funding regarding the seven papers in question. Okhluma et al., 2018 and Ramos-Garcia et al., 2020 were the only ones that did not consider any risk factors while conducting the study (cf. Table 10).

3. QUANTITATIVE EVALUATION

Of these 7 articles included (cf. Table 12), 9 (45%) significant associations of increased risk of cancer, out of 20, were found, meaning that the RR, OR, RRR, HR interval was higher than 1 (without it included) but nothing significant when extrapolated to the population (where there is no significant association). For oral cancer, this significant increase was found in Ohkuma et al. (2018), RRR = 1.13 ($p=0.009$), Ramos-Garcia et al. (2020), OR=1.32 ($p<0.001$), Dos Santos et al. (2022), HR=1.73 ($p<0.05$), Yan et al. (2021), RR=1.28 ($p<0.05$). For oral squamous cell carcinoma, a significant increase was observed for Ramos-Garcia et al. (2020), OR=1.41 ($p<0.001$). For oropharyngeal, the significant increase was depicted by Yan et al. (2021), RR=1.18 ($p<0.05$) and Dos Santos et al. (2022), HR=1.53 ($p<0.05$). Regarding head and neck cancer, the significant increase was showed by Dos Santos et al. (2022), HR=1.47 ($p<0.05$). For nasopharyngeal, it was found by Dos Santos et al. (2022), OR=1.40 ($p<0.05$).

The most robust evidence was seen in Gormley et al. (2022), for the relation with overall cancer ($RR_{\text{fixed effects}}$=1.22, 95%CI=1.16-1.29, $p<0.001$), with RR calculated using the fixed effects method (Table 12). The effect of the largest study included in each meta-analysis is also depicted in table 12.

Regarding heterogeneity (using the Q test) there were two meta-analyses with low heterogeneity (Gong, et al. 2015 and Franklin Sona, Mukete, et al. 2018), one (Ohkuma, et al. 2018) with nothing being mentioned and four with high heterogeneity (Ramos-Garcia, et al. 2020; Yan, et al. 2021; Dos Santos, et al. 2022 and Gormley, et al. 2022).

The only study retrieved from the 6th study (Dos Santos, et al. (2022) was the one of Tseng KS, et al. (2014) article (where we extracted the OR), because it was the only one from which the author of the systematic review drew information about the target population of the present review, results and association of interest (Diabetes Mellitus and Head and Neck cancer).

Table 9

Description of the 7 studies of diabetes mellitus and oral cancer association included in umbrella review, part I.

Study (year)	Journal	Population	Outcome	Sample size (patients)	Guidelines	PROSPERO code	Search strategy (date)	Eligibility criteria restrictions
Gong, et al. (2015)	Oral Oncology	Patients with diabetes mellitus type 2	Oral cancer and precancerous lesions	**17** studies total; **13** for oral cancer with **4,8** million participants and **6465** cases with oral cancer	MOOSE	ND	MEDLINE and EMBASE through May 31, 2014	a) original data from case-control or cohort studies; b) exposure was type 2 DM; c) outcome was oral cancers or precancerous lesions; d) studies should report either adjusted OR, RR, hazard ratio (HR), or standardized incidence/mortality ratios (SIR/ SMR) with their 95% Cis (or data to calculate them)
Franklin Sona, Mukete, et al. (2018)	Japanese Journal of Clinical Oncology	Type 1 Diabetes mellitus patients	Various types of cancer including head and neck	**15** observational studies with two case–control studies and **13** cohort studies from **11** articles	ND	ND	PubMed and EMBASE in April 2017	a) case–control studies and prospective or retrospective cohort studies; b) association between type 1 diabetes and the risk of cancer; c) reporting measures of outcomes with adjusted odds ratios (Ors) or relative risks (RRs) and 95% confidence intervals (Cis); d) data identical in more than one study or duplicated, the more comprehensive or first published study was included in the analysis.
Ohkuma, et al. (2018)	Diabetologia	Diabetes of type 1 or type 2	Cancer, overall and by site	**108** studies total, **19** million participants	PRISMA	ND	PubMed on 23 December 2016	a) Observational cohort studies if they had provided RR; b) exclusion if they had not adjusted at least for age or did not provide information about the variability around the point estimate or if they only had data for one sex; c) In duplicate reports from the same study, the one with the longest follow-up or the highest number of cases was included.
Ramos-Garcia, et al. (2020)	Oral Diseases	Diabetes of type 1 or type 2	Oral cancer or oral potentially malignant disorders	**52** studies, **559,927** participants	PRISMA	CRD42020162848	PubMed; Embase, Web of Science; Scopus; until November 2019	a)Original studies, without language, publication date, sex, or age restrictions; b)oral cancer in type 1 or type 2 DM; c) cohort, case-control and cross-sectional studies; d)exclusion of animal research or in vitro studies; e)results from the same study where included the most recent or with more data
Yan, et al. (2021)	Acta Diabetologica	Diabetes Mellitus type 2	Head and neck cancer subtypes	**27** studies, **1,4 million** T2DM cases and **23 045** HNC cases	PRISMA	ND	PubMed, Web of Science and Embase, on July 31, 2020	a) cohort or case–control study; b) exposure of T2DM; c) primary outcome was incidence of HNC, oral cancer, pharyngeal cancer, or laryngeal cancer; d) reported the risk estimates OR, standard incidence ratio (SIR), RR or hazard ratio (HR), and 95% confidence intervals;

Study (year)	Journal	Population	Outcome	Sample size (patients)	Guidelines	PROSPERO code	Search strategy (date)	Eligibility criteria restrictions
								e) when multiple articles come from the same, we only include the longest duration of follow-up.
Dos Santos, et al. (2022)	Head & neck, volume 44	Patients with systemic conditions	Oral squamous cell carcinoma	**95** studies total, **14442487** participants	PRISMA – PECOS	CRD42021242702	PubMed; Scopus; Web of Science; Embase; Google Scholar; OpenGrey; ProQuest Dissertation & Theses Global; on 27th February 2021 and updated on 19th February 2022	a) English articles; b) with systemic conditions; c) systemic conditions associated with increased risk to develop OSCC; d) observational studies
Gormley, et al. (2022)	BMJ Open	Metabolic disorders	Head and neck cancer	**36** studies total; **15** between diabetes type 2 and HNC	PRISMA	CRD42021250520	January 1966 to November 2021, including Cochrane Library, OVID SP versions of Medline and EMBASE; Cochrane Library, EthOS, Google Scholar, Open Grey and ClinicalTrials.gov (grey literature)	a) participants over 18 years old, of either sex, from any ethnic background; b) with T2D, obesity, dyslipidemia or hypertension; c) outcome HNSCC which may be human papilloma virus (HPV) positive or negative and high risk types HPV16, 18, 31 and 33 only will be included; d) All studies published from January 1966 in the English language; e) observational with head and neck squamous cell carcinoma; f) with OR or risk ratio, or data which will allow to calculate

Table 10

Description of the 7 studies of diabetes mellitus and oral cancer association included in umbrella review, part II.

Study (year)	Diagnostic criteria for Inclusion	Date of range of the studies included	Risk of bias	Meta-analysis	Risk factors	Funding
Gong, et al. (2015)	ND	1994 to 2013	Funnel plots and the further Begg's adjusted rank correlation and Egger' regression asymmetry tests	Yes	Cigarette smoking, alcohol consumption, betel-quid chewing and some types of viral infections	ND
Franklin Sona, Mukete, et al. (2018)	ND	1965 and 2014	funnel plots and the further Begg's adjusted rank correlation and Egger' regression asymmetry tests	Yes	Age; sex and age at onset of diabetes; alcohol; tobacco consumption; history of hepatitis; liver cirrhosis; BMI; history of cancer in first degree relatives; calendar year at follow-up; duration of diabetes and	ND

Study (year)	Diagnostic criteria for Inclusion	Date of range of the studies included	Risk of bias	Meta-analysis	Risk factors	Funding
					its status; period of diagnosis; socioeconomic status; region.	
Ohkuma, et al. (2018)	ND	1982 to 2016	Funnel plots and Egger's and Begg's tests	Yes	ND	ND
Ramos-Garcia, et al. (2020)	ND	1983 to 2016	Joanna Briggs Institute, University of Adelaide, Australia; QUIPS	Yes	ND	ND
Yan, et al. (2021)	ND	1994 to 2018	Egger's linear regression test and Begg's test;	Yes	Smoking, alcohol use or BMI/obesity.	ND
Dos Santos, et al. (2022)	ND	1961 to 2022	Joanna Briggs Institute; In the Diabetes Mellitus Study the risk of Bias is LOW	Yes	Having systemic conditions	ND
Gormley, et al. (2022)	Symptoms such as polyuria or polydipsia, plus: – A random blood plasma glucose concentration≥11.1 mmol/L. – A fasting plasma glucose concentration≥7.0 mmol/L (whole blood≥6.1 mmol/L). – Two-hour plasma glucose concentration≥11.1mmol/L, two hours after 75g anhydrous glucose in an oral glucose tolerance test. – Glycated hemoglobin (HbA1c) 6.5% or more (48 mmol/mol and above).	1992 to 2021	ROBINS-E	Yes	Smoking, alcohol and presence of human papillomavirus	ND

Table 11

Description of the 7 studies of diabetes mellitus and oral cancer association included in umbrella review, part III.

Study (year)	Association between diabetes and:	Nº of studies	Nº of cases/population	Countries in each revision
Gong, et al. (2015)	Oral cancer or precancerous lesions	**17** studies total; **13** for oral cancer and **4** for precancerous lesions	More than **4,8 million** patients and **6465** cases of oral cancer; **1407** cases with oral precancerous lesions (1137 with leukoplakia, 100 with erythroplakia and 170 with submucous fibrosis)	USA, Hungary, India, Poland, Germany, Italy, Japan, Switzerland, Denmark, England, Taiwan

Study (year)	Association between diabetes and:	Nº of studies	Nº of cases/population	Countries in each revision
Franklin Sona, Mukete, et al. (2018)	All types of cancer, including head and neck	**15** total, **2** with buccal cancer.	**31 893** cancer patients among a total of **1 915 179** participants	Sweden (n = 3), Australia (n = 2), UK (n = 2), Denmark (n = 2), Italy (n = 2), Finland (n = 1), Scotland (n = 1), US (n = 1) and Taiwan (n = 1)
Ohkuma, et al. (2018)	Lip, oral cavity, pharynx, head and neck, nasopharynx and oral cancer; and sex differences	**108** total; **3** with lip, oral cavity and pharynx; **3** with head and neck; **2** with nasopharynx; **2** with oral cancer	**108** total; **3** with lip, oral cavity and pharynx; **3** with head and neck; **2** with nasopharynx; **2** with oral cancer	USA, Japan, Italy, Denmark, Australia, Finland, Scotland, Sweden, Germany, Austria, Korea, China, Taiwan, Israel, UK, New Zealand, Singapure, Spain, Netherlands, Poland, France, Mauritius, Fiji, Nauru
Ramos-Garcia, et al. (2020)	Oral cancer in general or oral potentially malignant disorders	**52**; **28** studies only evaluated cancer; **23** reported data about prevalence and risk of oral cavity and oropharynx cancer	**559 927**	Asia (n = 21), Europe (n = 20), North America (n = 6), South America (n = 4) and Global Multicontinent (n = 1).
Yan, et al. (2021)	Oral cavity; pharynx; larynx; oral; head and neck general; specific squamous cell carcinoma; Nasopharyngeal	**27** total; all with DM2	**1.4** million T2DM cases and **23,045** HNC cases in 15 studies; **28,451** HNC cases in the remaining 12 studies.	Europe (n = 11), East Asia (n = 8), North America (n = 6), and Brazil (n = 1)
Dos Santos, et al. (2022)	Oral squamous cell carcinoma	**86** for qualitative synthesis; **9** for quantitative synthesis; **1** study with the Diabetes Mellitus condition	**1442487** patients with systemic conditions; **89089** with Diabetes Mellitus; Tseng: n(DM)=89530 and n(without DM)=**89530**	Japan, United States, Denmark, Taiwan and South Korea.
Gormley, et al. (2022)	Head and neck squamous cell carcinoma	**36** total, **15** with diabetes mellitus type 2	**39002** total; **17582** cases with diabetes mellitus	Sweden, UK, USA, Netherland, European, Denmark, Israel, Taiwan, Scotland, Japan, Finland, Korea, China, Hawaii

Table 12

Data on the associations found on the 7 studies of diabetes mellitus and oral cancer association included in umbrella review, and tools for bias and heterogeneity evaluation.

Study (year)	Association between diabetes mellitus and	Random effects	Largest Study of our Outcome	Random p-value	Egger's p-value	I^2; p-value	Evidence of reclassification (I-IV)	AMSTAR
Gong, et al. (2015)	oral cancer	SRR = 1.15 (95% CI: 1.02–1.29)	Wotton/2011/ England: ORLS1 = 1.04 (0.63-1.63); ORLS2 = 0.95 (0.43-1.84)	p = 0.277	Egger's p = 0.176; Begg's p = 0.392	p = 0.277, I^2 = 15.4%	The quality scores ranged from 5 to 9, with the median score 7. Most of the included studies (13/17) were of high quality (NOS score ⩾ 7).	Newcastle-Ottawa quality assessment Scale (NOS)
Franklin Sona, Mukete, et al. (2018)	buccal cancer	OR ou RR = 1.79 (0.96–3.36)	ND	ND	p = 0.218	I^2 = 0.0%	One of the studies was qualified as Low (Zendehdel et al., 2003) and the other one High (Hemminki et al., 2016)	Newcastle-Ottawa Scale (NOS)

Study (year)	Association between diabetes mellitus and	Random effects	Largest Study of our Outcome	Random p-value	Egger's p-value	I^2; p-value	Evidence of reclassification (I-IV)	AMSTAR
Ohkuma, et al. (2018)	lip, oral cavity, pharynx cancer	RRR = 0.94 (0.68-1.32);	Oral OR = 1.13 (1.00-1.28)	ND	Egger's p = 0.13; Begg's p = 0.16	ND	Lower score (<7 points)=1.02 (0.97-1.07) Higher score (≥7points)=1.07 (1.04−1.10)	Newcastle-Ottawa Quality Assessment Scale (NOS)
	head and neck cancer	RRR = 1.01 (0.59-1.72);		ND		ND		
	nasopharynx cancer	RRR = 1.04 (0.92-1.18);		ND		ND		
	oral cancer	RRR = 1.13 (1.00-1.28)		p = 0.009		ND		
Ramos-Garcia, et al. (2020)	oral cancer	OR=1.32 (1.12-1.56) I^2=75.5%	Mixed OR = 1.21 (0.95–1.53)	p < 0.001	P = 0.492	I^2 = 75.5%; P < 0.001	"low" quality of evidence for the association between oropharyngeal cancer development and diabetes; and "very low" quality of evidence for the rest of analyzed outcomes. The most influential domain was "inconsistency," mainly due to the high heterogeneity found.	GRADE
	oral squamous cell carcinoma	OR=1.41 (1.1-1.81) I^2=83.2%		p < 0.001				
	oropharyngeal cancer	OR=1.17 (0.82-1.65) I^2=32.2%		p = 0.229				
	mixed	OR=1.21 (0.95;1.53) I2=41.7%		p = 0.127				
Yan, et al. (2021)	head and neck cancer	RR = 1.04 (95% CI: 0.88-1.23); p=0.635;	head and neck squamous cell carcinoma = 0.92 (0.88-0.96)	p < 0.10	Egger's p = 0.437; Begg's p = 0.951	P < 0.001; I^2 = 83.2%	ND	Newcastle-Ottawa Quality Assessment Scale (NOS)
	oral cancer	RR = 1.28, (95% CI, 1.04-1.58);		p < 0.05			ND	
	oropharyngeal cancer	RR = 1.18, (95% CI, 1.02–1.37)		p < 0.05			ND	
Dos Santos, et al. (2022)	head and neck cancer	HR = 1.47 (1.30-1.66) *	ND	p<0.05	ND	p < 0.01, I^2 = 95%	87%, low risk of bias	Joanna Briggs Institute
	oral cancer	HR = 1.73 (1.46-2.05) *		p<0.05				
	oropharyngeal cancer	HR = 1.53 (1.01-2.31) *		p<0.05				
	nasopharyngeal carcinoma	OR = 1.40 (1.03-1.90) *		p<0.05				
Gormley, et al. (2022)	overall cancer	$RR_{overall}$=1.13, 95%CI=0.95-1.34; $RR_{fixed\ effects}$=1.22, 95%CI=1.16-1.29	Lo 2013 OR = 1.21 (1.13-1.30)	p <0.001	ND	p < 0.0001, I^2= 80.0%	One study was rated as 'Very high' risk of bias (3.7%), 21 studies were rated as 'High' (77.8%), one study as 'Some concerns' (3.7%) and the remaining studies as 'Low' (14.8%) risk of bias	ROBINS-E tool
	oral cancer	RR= 1.13, 95%CI (0.97-1.31)	Seo 2020 OR = 1.10 (0.98-1.24)	ND				
	oropharyngeal cancer	RR= 1.16, 95%CI(0.73-1.83)	Saarela 2019 OR = 0.95 (0.84-1.08)	ND				

*Data collected from the Tseng KS, et al. (2014) - article within the principal one.

There was no evidence for the presence of small study effects according to Egger's test (cf. Table 12), except for incidence of endometrial and hepatocellular cancer, where P<0.10 with more conservative effects in the larger studies.

4. Risk of Bias

As can be seen in table 13, all the studies were assessed with a score of high quality, three studies with nine positive answers, two with all 10 positive questions and two studies with eight positive answers.

Table 13

Risk of bias evaluation with a critical appraisal checklist for the systematic reviews (according to Aromataris et al., 2021)

	Dos Santos et al. (2022)	**Ramos-Garcia et al. (2020)**	**Ohkuma et al. (2018)**	**Yan et al. (2021)**	**Gormley et al. (2022)**	**Gong et al. (2015)**	**Franklin Sona, Mukete et al. (2018)**
Is the review question clearly and explicitly stated?	Met	Met	Met	Met	Met	Met	Met
Were the inclusion criteria appropriate for the review question?	Met	Met	Met	Met	Met	Met	Met
Was the search strategy appropriate?	Met	Met	Met	Met	Met	Met	Met
Were the sources and resources used to search for studies adequate?	Met	Met	Met	Met	Met	Met	Met
Were the criteria for appraising studies appropriate?	Met	Met	Met	Met	Met	Met	Met
Was critical appraisal conducted by two or more reviewers independently?	Met	Met	Unclear	Met	Met	Met	Met
Were the methods used to combine studies appropriate?	Met	Met	Met	Met	Met	Met	Met
Was the likelihood of publication bias assessed?	Met	Met	Met	Met	Met	Met	Met
Were recommendations for policy and/or practice supported by the reported data?	Met	Met	Met	Unclear	Met	Met	Unclear
Were the specific directives for new research appropriate?	Not Met	Met	Met	Unclear	Not met	Met	Not met
Include? Low, Moderate or High quality?	**Yes High**	**Yes High**	**Yes High**	**Yes High**	**Yes High**	**Yes High**	**Yes High**

5. Strategy for Data Synthesis

Study double counting in different systematic reviews were presented visually using the Graphical Representation of Overlap for OVErviews (GROOVE) tool (cf. Table 14). This methodological approach facilitates the assessment of overlap of primary studies among multiple systematic reviews.

It was observed that both Yan, P et al. (2021) and Gong, Y et al. (2015) had the highest percentage of overlapped studies with Ramos-Garcia et al. (2019) with 61.1% and 64.3%, respectively. On the other hand, Sona, M. et al. (2018) does not have any articles in common with the rest of the systematic reviews in question.

Table 14

Graphical Representation of the Overlap for OVErviews (GROOVE)

	Ramos - Garcia et al. (2019)	dos Santos et al. (2022)	Yan et al. (2021)	Gong et al. (2015)	Ohkluma et al. (2018)	Gormley. et al. (2022)
dos Santos et al. (2022)	7.7%					
Yan et al. (2021)	61.1%	6.3%				
Gong et al. (2015)	64.3%	0.0%	36.8%			
Ohkluma et al. (2018)	12.5%	0.0%	10.5%	15.4%		
Gormley et al. (2022)	5.3%	14.3%	27.8%	0.0%	33.3%	
Sona et al. (2018)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

21	=	**Total nodes (pairs of reviews)**
9	=	Slight overlap (<5%)
3	=	Moderate overlap (5% to <10%)
3	=	High overlap (10% to <15%)
6	=	Very High overlap (≥15%)

V. DISCUSSION

In this section we are going to discuss the relevance and the mechanisms of the association between Diabetes Mellitus and Cancer.

Diabetes can influence the neoplastic process through various pathophysiological hypotheses, including hyperinsulinemia (either endogenous due to insulin resistance or exogenous due to the administration of insulin or insulin secretagogues), hyperglycemia or chronic inflammation based on biological mechanisms, particularly hormonal ones, involving insulin resistance (Morss, & Edelman, 2007; Richardson & Pollack, 2005). This hypothesis is proved by studies that show that treatment with metformin, an insulin sensitizer, is associated with a lower incidence of cancer in diabetic patients rather than insulin or sulphonylurea therapy (Giovannucci et al., 2010; Noto et al., 2010).

Some other studies suggest that waist circumference, waist-to-hip ratio or direct measures of visceral adiposity are associated with risk for cancer, regardless of Body Mass Index (BMI) (Giovannucci et al., 2010).

Individuals with type 1 diabetes, who have an insulin deficit, have a lower risk of cancer than individuals with type 2 diabetes (Noto et al., 2010).

Type 2 diabetes is characterized by insulin resistance and secondary hyperinsulinemia (caused by being obese and inactive). The reduced insulin sensitivity is fundamental because it induces compensatory hyperinsulinemia with an increased level of circulating insulin-like growth factors (IGF) - which stimulates a mitogenic effect in many organs increasing risk of cancer, that works in a way such as the IGF receptors form a complex network which mediate insulin and IGF responses. Most cancer cells express the A isoform of the insulin receptor and this can stimulate insulin-mediated mitogenesis (Noto et al., 2010). Multiple signaling pathways are activated and once that happens, these can stimulate multiple cancer phenotypes, including proliferation, protection against apoptotic stimuli, invasion and metastasis, potentially increasing the promotion and progression of many types of cancer cells. Oxidative stress and chronic inflammation caused by the hyperinsulinemia are present for a considerable period of time before the DM, properly said, and continue in a self-perpetuating cycle throughout its evolution. A reduced latency period or the nonexistence of a consistent pattern of duration would perpetuate the sharing of risk factors, like hyperinsulinemia, as a connection between diabetes and cancer. On the contrary, a lasting latency period or a consistent pattern of

duration of diabetes and cancer would imply that diabetes itself is a risk factor for the development of cancer (Giovannucci et al., 2010).

How I mentioned before, there is an amount of hypothesis for this association, one of them is related to the increased circulating insulin who brings a cutback in hepatic synthesis and blood levels of globulin, which boost the bioavailable estrogen both in men and women and also increases the levels of bioavailable testosterone in this last ones. Ovarian androgen synthesis is increased by hyperinsulinemia in premenopausal women. All this is related to the fact that high levels of endogenous sex steroids are directly associated with an enhanced risk of cancer in postmenopausal women (Giovannucci et al., 2010).

Another hypothesis is based in the mechanism of the adipose tissue, an active endocrine organ that produces interleukin-6 (IL-6), adiponectin, monocyte chemoattractant protein, plasminogen activator inhibitor-1 (PAI-1), leptin and tumor necrosis factor-α. All these factors can play a fundamental role in the regulation of malignant transformation or cancer progression. Activation of the signal transducer and activator of transcription (STAT) protein signaling, by means of cytokines such as IL-6, is known to increase the proliferation of cancer cells, while suppressing the hosts anti-tumor immunity (Giovannucci et al., 2010).

On another hand, the pro-proliferative molecular pathways that hyperinsulinemia activates is based in the upregulation of the oncogenic c-terminal cyclin D1 (CCND1) (activation and its protein cyclin D1) play a crucial part in the pathogenesis of oral cancer, will not only increasing the proliferation but also helping the migration of the malignant cells (Okumura et al., 2002).

Finally, still about the type of hypothesis, hyperglycemia is capable of provoking oxidative stress with DNA damage due to free radical release. Furthermore, the increase in glucose consumption by tumor cells, known as the Warburg effect, enhances cell proliferation mediated by the activation of glucose transporters 1 (GLUT-1) and Protein kinase C alpha (PKC-α) (Okumura et al., 2002).

In addition to an increased risk of cancer incidence, there is now considerable evidence in the literature suggesting that patients with Diabetes have a lower cancer screening and survival rate than patients without. Barone et al. 2008 evaluated 23 studies and found that DM was associated with reduced cancer-specific survival.

In 2010, the American Diabetes Association and the American Cancer Society (ACS) presented a consensus report suggesting that the incidence of cancer is associated with DM and that a healthy diet, physical activity and weight management can reduce the risk and improve the outcomes of DM and some forms of cancer.

This relationship is bidirectional: diabetes can develop as a consequence of cancer, since cancers generally cause insulin resistance and subsequent hyperglycemia through the production of cytokines such as tumor necrosis factor-α, as mentioned above (American Cancer Society [ACS]).

This umbrella review examined the current evidence from meta-analyses on the association between Diabetes Mellitus and head and neck cancer. Most articles demonstrated positive results for the risk being higher in people with diabetes rather than without.

A number of reasons for the association between these two conditions appear in some studies and not in others:

- The smaller sample sizes when there is little to nonsignificant association because, this error incurred by assessing only part of the population. There are 2 more factors linked to this: the variability of the sample units within the population, which means having a representative sample of the population to be studied, and the method of selecting the sample units;
- The different region of each study, understanding that the landforms, climatic phenomena, social composition and human habits are different in distinct places, which inclines the population to different susceptibilities to certain diseases;
- The risk factors, because some are more predisposed to causing the result than others, such as tobacco and alcohol, added to the equation with Diabetes Mellitus, will automatically make the individual more susceptible to developing cancer than one who only has Diabetes and a high BMI.
- There are many modifiable and non-modifiable risk factors shared between type 2 diabetes and cancer, including age and sex, obesity, physical activity, diet, alcoho and smoking. Between the modifiable factors, the most important ones are having systemic conditions (Dos Santos, et al. 2022); alcohol, tobacco, history of hepatitis,

liver cirrhosis, BMI, follow-up, duration of diabetes and its status and region (Sona, et al. 2018), because their RR or OR or HR are superior from the remaining.

VI. CONCLUSION

Regarding the question “Is there a relationship between diabetes mellitus and head and neck carcinoma?” the result of this umbrella review concludes there is support for listing Diabetes Mellitus as a risk factor associated with Head and Neck cancer, even though larger studies are needed to validate the scientific evidence in this regard. There is positive data seen in nine out of the twenty associations present in our seven articles, specifically regarding oral cancer overall with the highest number of correlations found and the most robust evidence. Although it was possible to see this association, studies in general are not viable to be compared because of the fact that the variables are different between them.

It is concerning that only a few published studies are available for this association, being that diabetes and cancer are very frequent diseases in society, so there should be a large amount of data to be collected. If hospital records were more easily accessible it could generate superior and higher quality associations between type 2 diabetes and oral cancer but, unfortunately, only a part of them were assessed and a smaller fraction is published. A part, and because of this, it is never known if the data used is the most genuine and strongest one, which can be one of the main hypotheses for the bias.

Furthermore, given the limitations of the included quantitative systematic reviews, it is important to continue conducting studies, collecting data following the same structure for all types of head and neck cancer, but with better control of risk factors. So, the future articles and research should be done following the same guidelines, such as better assessment of type 2 diabetes itself, the treatment duration and circumstances like risk factors, in order to draw more precise conclusions on the topic.

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