EGAS MONIZ SCHOOL of HEALTH & SCIENCE | INSTITUTO UNIVERSITÁRIO EGAS MONIZ

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MESTRADO INTEGRADO EM MEDICINA DENTÁRIA

TO WHAT EXTENT HAS THE EPIDEMIOLOGY OF CANCER CHANGED IN PORTUGAL?

Trabalho submetido por
Noha Regili
para a obtenção do grau de Mestre em Medicina Dentária

Junho de 2025

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Mestre Pedro Trancoso

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DEDICATION

À vous, Mamie et Jidy, j'aurais aimé que vous soyez présents pour ce moment si important. Mais j'espère que de là où vous êtes, vous êtes fiers de voir votre petite-fille devenir docteur.

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RESUMO

O cancro oral é um importante problema de saúde pública, devido à sua crescente incidência em todo o mundo. Inclui principalmente os cancros dos lábios e da cavidade oral e também o cancro da orofaringe, que se encontram entre as formas mais comuns de cancro da cabeça e do pescoço. A maioria destes cancros é diagnosticada numa fase avançada, o que reduz consideravelmente as hipóteses de sobrevivência dos doentes. O diagnóstico tardio deve-se frequentemente à ausência de sintomas precoces e à falta de sensibilização.

Os principais factores de risco estão bem estabelecidos: o consumo de tabaco e de álcool, os comportamentos sexuais de risco, a exposição ao HPV (nomeadamente ao subtipo 16), uma higiene oral deficiente, uma alimentação desequilibrada, a exposição a certas substâncias cancerígenas, como a noz de areca ou o mate, e determinantes socioeconómicos que desempenham um papel crucial no acesso ao rastreio e aos cuidados.

O objetivo desta tese é estudar a evolução epidemiológica do cancro oral em Portugal ao longo de um período de doze anos, entre 2010 e 2022. A análise baseia-se em dados provenientes de bases de dados oficiais como o GLOBOCAN e o ECIS. Os indicadores avaliados incluem a incidência (número de novos casos), a prevalência (número total de casos existentes) e a mortalidade (número de óbitos por cancro).

Para enriquecer esta avaliação, é efetuada uma comparação com os dados de Franca, bem como com os dados de outras regiões do mundo, como a Europa no seu conjunto, os Estados Unidos e a Ásia. Esta abordagem comparativa permite uma melhor compreensão das especificidades nacionais e identifica os factores que influenciam as variações geográficas no peso do cancro oral.

A comparação mostra uma situação mais grave em França do que em Portugal, uma melhoria nos Estados Unidos e taxas elevadas na Ásia, sublinhando a importância de abordagens preventivas adaptadas a cada região.

Palavras-chaves: cancro oral, incidência, prevalência, mortalidade

ABSTRACT

Oral cancer is a major public health issue, due to its growing incidence worldwide. It mainly comprises cancers of the lip and oral cavity and oropharyngeal cancer, which are among the most frequent forms of head and neck cancer. Most of these pathologies are diagnosed at an advanced stage, which considerably reduces patients' chances of survival. Late diagnosis is often due to a lack of early symptoms and awareness.

The main risk factors are well established: tobacco and alcohol consumption, risky sexual behavior, exposure to HPV (particularly subtype 16), poor oral hygiene, unbalanced diet, exposure to certain carcinogenic substances such as areca nuts or mate, and socio-economic determinants playing a crucial role in access to screening and care.

The aim of this work is to study the epidemiological evolution of oral cancer in Portugal over a twelve-year period, between 2010 and 2022. The analysis is based on data from official databases such as GLOBOCAN and ECIS. Indicators assessed include incidence (number of new cases), prevalence (total number of existing cases) and mortality (number of deaths due to cancer).

To enrich this assessment, a comparison was made with France, as well as with data from other regions of the world, such as Europe as a whole, the United States and Asia. This comparative approach enables us to better understand national specificities and identify factors influencing geographical variations in the burden of oral cancer.

Comparisons show a more serious situation in France than in Portugal, an improvement in the United States, and high rates in Asia, underlining the importance of preventive approaches tailored to each region.

Key words: oral cancer; incidence; prevalence; mortality

RESUME

Le cancer oral constitue un enjeu de santé publique important, en raison de son incidence croissante à l'échelle mondiale. Il regroupe principalement les cancers de la cavité buccale et de l'oropharynx, qui figurent parmi les formes les plus fréquentes des cancers de la tête et du cou. Ces pathologies sont majoritairement diagnostiquées à un stade avancé, ce qui réduit considérablement les chances de survie des patients. Le diagnostic tardif s'explique souvent par une absence de symptômes précoces et un manque de sensibilisation.

Les principaux facteurs de risque sont bien établis : consommation de tabac et d'alcool, comportements sexuels à risque, exposition au HPV (en particulier le sous-type 16), mauvaise hygiène bucco-dentaire, alimentation déséquilibrée, exposition à certaines substances cancérigènes comme les noix d'arec ou le maté, et enfin des déterminants socio-économiques jouant un rôle crucial dans l'accès au dépistage et aux soins.

Cette thèse a pour objectif d'étudier l'évolution épidémiologique du cancer oral au Portugal sur une période de douze ans, entre 2010 et 2022. L'analyse s'appuie sur les données des bases de données officielles telles que GLOBOCAN et ECIS. Les indicateurs évalués comprennent l'incidence (nombre de nouveaux cas), la prévalence (nombre total de cas existants) et la mortalité (nombre de décès dus au cancer).

Afin d'enrichir cette évaluation, une comparaison réalisée avec les données françaises, ainsi qu'avec celles d'autres régions du monde telles que l'Europe dans son ensemble, les États-Unis et l'Asie. Cette approche comparative permet de mieux comprendre les spécificités nationales et d'identifier les facteurs influençant les variations géographiques du fardeau du cancer oral.

La comparaison montre une situation plus grave en France qu'au Portugal, une amélioration aux États-Unis, et des taux élevés en Asie, soulignant l'importance d'approches préventives adaptées à chaque région.

Mots-clés : cancer oral, incidence, prévalence, mortalité

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List of abbreviations:

AJCC: American Joint Committee on Cancer

CRP: C-reactive protein

CRT: Chemoradiation therapy

CT: Chemotherapy

DOI: Depth of invasion

ENE: Extranodal extension

GBO: The Global Cancer Observatory

GY: Gray

HPV: Human papillomavirus

IARC: The International Agency on Research for Cancer

IL: Interleukin

ISH: *In situ* hybridization

OED: Oral epithelial dysplasia

OC: Oral cancer

OPSCC: Oropharyngeal squamous cell carcinoma

OSCC: Oral squamous cell carcinoma

PAHs: Polycyclic aromatic hydrocarbons

PCR: Polymerase chain reaction

POH: Poor oral hygiene

QPCR: Quantitative polymerase chain reaction

ROS: Reactive oxygen species

SLT: Smokeless tobacco

TSNAs: Nitrosamines

UICC: The International Union Against Cancer

WHO: World Health Organization

Introduction

The estimated annual new cases of oral and lip cancer are close to 390 000 and 106 400 new cases for oropharynx cancer. Indeed, oral cancer (OC) is a worldwide health problem with an incidence and mortality rate that continues to rise.
Among those OCs, oral squamous cell carcinoma (OSCC) is the most common entity representing more than 90% of the malignancies (M.S.Rini et al., 2019),

The World Health Organization (WHO) named the precancerous occurrence as oral potentially malignant disorder, a condition that may or not exhibit epithelial dysplasia on histopathologic evaluation (Yang.G., 2022).
The tongue and floor of the mouth are the sites most frequently affected. Yet, OC can originate in any location of the mucosa. Even though men between 50 and 60 years old are the most affected, the incidence rate in younger patients is rising, particularly for oropharyngeal cancer. (Melo.B et al., 2020).

The main etiological factors are tobacco even if in passive form and alcohol use among others such as betel quid and diet (Montero.P., 2015). Sexual behavior and exposure to human papillomavirus (HPV), primarily HPV-16 are also considered risks for oropharyngeal squamous cell carcinoma (OPSCC) (Melo.B et al., 2020).

Hence, an early diagnosis is important as the more advanced the stage of cancer at diagnosis is, the lower the response rate to therapy will be. Moreover, with high stages patients have a higher risk of developing metastases and relapses (Russo.D., 2018).
Unfortunately, those cancers are frequently undiagnosed until symptomatic, which means that the disease is already at an advanced stage. Thanks to numerous tests such as biopsy which is the gold standard diagnostic exam (Vyas.T., 2018); and others such as oral autofluorescence or toluidine blue staining that may help the clinician regarding the more appropriate site to perform the biopsy, diagnosis can be made quickly and easily (Chhabra.N et al., 2014).

Treatment of OC is usually surgical followed by radiotherapy but new chemotherapy (CT) agents and changes in surgical timing and techniques may potentially increase survival rates. In the case of oropharyngeal cancer whose stages are more advanced at the

time of diagnosis the treatment is managed with radiotherapy or chemoradiation therapy (CRT). (Parmar.A., 2021)

In 2018, in Portugal, there were 893 new cases of oral cavity cancer and 341 new cases of oropharyngeal cancer.
In France, 4 677 new cases of oral cavity cancer and 4 993 cases of oropharyngeal cancer were recorded.
Thus, the aim of this study is to analyze the numbers published in official databases, both by the European Union and the WHO. And, to understand whether the epidemiological data regarding the incidence, prevalence and mortality of OC have changed both in Portugal and France while comparing the situation in both countries with European, American and Asian data.

1. Oral and Oropharyngeal cancer

Oral and oropharyngeal cancers are two of the most common cancers located in the head and neck region. With more than 300 000 new cases each year, of which more than 100 000 are oropharyngeal cancer, (GLOBOCAN.,2022) the OSCC and the OPSCC are the 6th most common malignant tumors in the world. (Russo.D et al., 2018)

Because most cases are diagnosed late, management can be complex, which is why it's important to pay attention to any alterations of the oral cavity.

1.1. Anatomy

The oral cavity extends superiorly from the lips to the junction between the hard and soft palates, and inferiorly to the circumvallate papillae of the tongue. It then extends further to the oropharynx. Moreover, it is divided into several anatomical regions: lip, tongue, floor of mouth, buccal mucosa, upper and lower gum, retromolar trigone and hard palate (figure 1) (Montero.P et al., 2015).

The dentist plays a huge role in identifying abnormalities as this region needs to be thoroughly evaluated. For instance, anatomical variations, although most of the time harmless, remain quite frequent and thus call for a thorough inspection that must be performed by the former to detect potentially malignant and/or malignant lesions as early as possible (Souza.P et al., 2023). Among these potentially malignant lesions we find leukoplakia the most common.

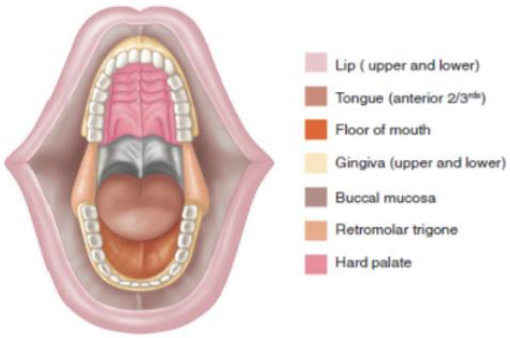


Figure 1. Anatomic site of the oral cavity. (Shah JP, Patel SG, Singh B, et al; 2012)

1.2. Histopathology

The TNM classification system was developed by a French oncologist, Pierre Denoix, between 1943 and 1952. Dr. Denoix aimed to create a universal language for collecting information about a patient's oncological status and prognosis by considering the anatomical extent of the tumor. This system is based on three parameters: tumor characteristics (T), the presence or absence of regional lymph node metastases (N), and the presence or lack of distant metastases (M) (Dulguerov.S., 2017).

The International Union Against Cancer (UICC) adopted this system in 1954, while the American Joint Committee on Cancer (AJCC) was established in 1958. For 25 years, the AJCC and UICC worked independently on their classification systems. It was only in 1987 that the first joint AJCC/UICC TNM classification was introduced. (Karassawa.D et al.,2020).

In 2017, the 8th edition of the TNM classification was published, incorporating several modifications. For instance, in the T category, the concept of depth of invasion (DOI) was introduced for the primary tumor (Table 1). In the N category, extranodal extension (ENE) was included (Table 2), although p16-positive oropharyngeal cancers were excluded. Additionally, a specific section was added for staging HPV-related (p16-positive) oropharyngeal cancer (Karassawa.D et al., 2020).

The correlation between poor prognosis and tumor thickness has been recognized for a long time now. The latter is measured as the perpendicular distance from the most

superficial point of the tumor surface to the deepest point of tumor invasion. Nowadays, DOI, also known as “reconstructed tumor thickness”, is considered a more relevant measure (Lacheretz-Szablewski.V et al., 2022).

According to the new AJCC staging system, DOI measurements first identify the "horizon" of the basement membrane of the adjacent squamous mucosa. A perpendicular “plumb line” is then drawn from the horizon to the deepest point of tumor invasion (Kato.M., 2020). It is essential to distinguish between exophytic and ulcerated tumors, as DOI is typically smaller than tumor thickness in exophytic tumors, whereas it is larger in ulcerated tumors (Lacheretz-Szablewski.V et al., 2022). DOI can be estimated through palpation and imaging, but histological examination is indispensable for accurate measurements (Kato.M., 2020). In the 8th edition TNM classification, tumors previously classified as T1 are reclassified as T2 if the DOI exceeds 5 mm and as T3 if it exceeds 10 mm (Ghantous.Y et al., 2022).

ENE was added as a prognostic variable for locoregional lymph node metastases, along with the size and number of metastatic lymph nodes. ENE significantly impacts the prognosis of head and neck cancers, except in HPV-related p16-positive cancers. For clinical staging, radiological examination alone is insufficient. Physical examination and specific signs such as skin invasion, muscle infiltration, attachment to adjacent structures, or dysfunction of cranial nerves, the brachial plexus, or the phrenic nerve supported by radiological evidence are necessary to determine ENE positivity. Pathological ENE is defined as the extension of metastatic carcinoma within a lymph node through the fibrous capsule into the surrounding connective tissue, regardless of stromal reaction. ENE is categorized as minor (ENEmi) if the extension is ≤2 mm beyond the capsule and major (ENEma) if it is visible to the naked eye or >2 mm (Table 3) (Lydiatt.W et al., 2017).

The p16-positive variant was also introduced in the 8th TNM classification. HPV-positive OPSCCs have a better response to cancer treatment and higher survival rates due to their distinct oncogenic mechanisms. HPV-positive patients are typically younger and have no history of alcohol or tobacco use. P16 positivity is associated with a lower T stage and a higher N stage compared to HPV-negative cancers. The higher N stage is due to early lymph node involvement caused by the lack of subepithelial connective tissue layers in the tonsillar crypt epithelium. Tumor cells migrate to lymph nodes before the

primary lesion becomes large enough to be detected. Key changes in the classification include the removal of the T0 stage for p16-positive cases and the union of T4a and T4b into a single T4 category (Table 4). For the N stage, ipsilateral lymph nodes <6 cm are classified as N1, bilateral or contralateral lymph nodes <6 cm as N2, and lymph nodes >6 cm as N3 (Table 5) (Table 6) (Machczyński.P et al., 2020).

Histopathological evaluation is essential for diagnosis and reveals different features between HPV-positive and HPV-negative OPSCC. The squamous epithelium is the primary target in oropharyngeal carcinomas, and tumor cells have a high nucleus-to-cytoplasm ratio, oval to spindle-shaped nuclei, and syncytial cytoplasm, giving a basaloid appearance.

However, the progression from dysplasia to invasive growth is not observed in HPV-positive OPSCC, unlike HPV-negative carcinomas. This complicates the diagnosis of precancerous lesions and the assessment of cancer risk (Ferris.R, Westra.W., 2023).

Table 1. Primary tumor (T) defintion of oral cancer. Adapted from (Amin et al.2017)

TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor ≤ 2 cm and DOI ≤ 5 mm
T2	Tumor ≤ 2 cm, DOI > 5 mm and ≤ 10 mm ***or*** tumor > 2 cm and ≤ 4 cm and DOI ≤ 10 mm
T3	Tumor > 4 cm ***or*** any tumor with DOI > 10 mm
T4 **T4a** **T4b**	Tumor invades adjacent structures only (e.g., through cortical bone of mandible or maxilla, or involves the maxillary sinus or skin of the face) Tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery

Table 2. Clinical assessment of regional lymph nodes (cN). Adapted from (Amin et al.2017)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm and ENE-
N2 **N2a** **N2b** **N2c**	Metastasis in a single ipsilateral lymph node > 3 cm and ≤ 6 cm and ENE-; ***or*** metastases in multiple ipsilateral lymph nodes, ≤ 6 cm and ENE-; ***or*** in bilateral or contralateral lymph nodes, ≤ 6 cm and ENE- Metastasis in a single ipsilateral lymph node > 3 cm and ≤ 6 cm and ENE- Metastases in multiple ipsilateral lymph nodes, ≤ 6 cm and ENE- Metastases in bilateral or contralateral lymph nodes, ≤ 6 cm and ENE-
N3 **N3a** **N3b**	Metastasis in a lymph node > 6 cm and ENE-; ***or*** metastasis in any lymph node(s) with ENE+ clinically Metastasis in a lymph node > 6 cm and ENE- Metastasis in any lymph node(s) with ENE+ clinically

Table 3. Pathological assessment of regional lymph nodes (cN). Adapted from (Amin et al.2017)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm and ENE-
N2 **N2a** **N2b** **N2c**	Metastasis in a single ipsilateral lymph node, ≤ 3 cm and ENE+; ***or*** metastasis in a single ipsilateral lymph node > 3 cm and ≤ 6 cm and ENE-; ***or*** metastases in multiple ipsilateral lymph nodes, ≤ 6 cm and ENE-; ***or*** in bilateral or contralateral lymph nodes, ≤ 6 cm and ENE- Metastasis in a single ipsilateral lymph node, ≤ 3 cm and ENE+; ***or*** metastasis in a single ipsilateral lymph node > 3 cm and ≤ 6 cm and ENE- Metastases in multiple ipsilateral lymph nodes, ≤ 6 cm and ENE- Metastases in bilateral or contralateral lymph nodes, ≤ 6 cm and ENE-
N3 **N3a** **N3b**	Metastasis in a lymph node > 6 cm and ENE-; ***or*** metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE+; ***or*** multiple ipsilateral, contralateral, or bilateral nodes, any with ENE+; ***or*** a single contralateral node of any size and ENE+ Metastasis in a lymph node > 6 cm and ENE- Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE+; ***or*** multiple ipsilateral, contralateral, or bilateral nodes, any with ENE+; ***or*** a single contralateral node of any size and ENE+

Table 4. Primary tumor (T) defintion for HPV-related (p16 positive) oropharyngeal cancers. Adapted from (Amin et al.2017)

T0	No tumor identified, but p16+ cervical node(s) involvement
Tis	Carcinoma *in situ*
T1	Tumor ≤ 2 cm
T2	Tumor > 2 cm and ≤ 4 cm
T3	Tumor > 4 cm or extension to lingual surface of the epiglottis
T4	Moderately advanced local disease; tumor invades larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond

Table 5. Clinical assessment of regional lymph nodes (cN) in HPV-related (p16 positive) oropharyngeal cancers. Adapted from (Amin et al.2017)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes ≤ 6 cm
N2	Contralateral or bilateral lymph nodes ≤ 6 cm
N3	Lymph node(s) > 6 cm

Table 6. Pathological assessment of regional lymph nodes (pN) in HPV-related (p16 positive) oropharyngeal cancers. Adapted from (Amin et al.2017)

pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in 4 or fewer lymph nodes
pN2	Metastases in more than 4 lymph nodes

The majority of OSCC arise from pre-existing oral epithelial dysplasia (OED); however, the transformation of OED into OSCC is not yet fully understood. Studies have shown that chromosomal alterations are present in OSCC. Specifically, somatic mutations in several genes, including NOTCH1, KMT2D, CASP8, AJUBA, NSD1, HLA-A**,** and TGFBR2, have been identified. The increased chromosomal instability associated with these mutations significantly increased the probability of OSCC development (Odell.E et al., 2021)(Woo.SB., 2019)(De Freitas Silva.BS et al., 2021). A key diagnostic criterion for carcinoma is the invasion of epithelial cells through the basement membrane into the superficial connective tissues. Under the microscope, OSCC is distinguishable by its invasive components, characterized by the presence of tumor nests within the deeper layers beneath the surface epithelium (Figure 2) (Speight, Farthing, 2018).

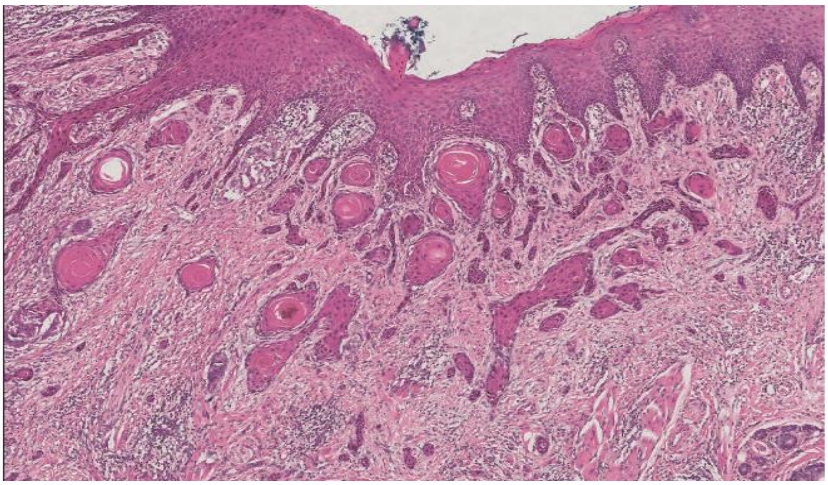


Figure 2. Squamous cell carcinoma of the oral cavity. Tumor islands can be seen infiltratinng connective tissues deep to the overlying oral epithelium. This carcinoma is moderately differenciated with a non-cohesive invasive pattern. (Speight, Farthing., 2018)

During microscopic examination, the pathologist must systematically grade the tumor, as this is directly associated with the prognosis. Several grading systems are recognized, including Broder's system (1927), Bryne's system (1988, 1992), and the WHO system, which is partly based on Broder's.

Broder's system categorizes tumors into four grades based on the differentiation of tumor cells. While this system is not suitable for predicting lymph node metastases or prognosis, it can be used to assess histological differentiation to help predict the tumor type. (Table 7)

Table 7. Broder's quantitative histological grading system based on the differenciation of malignant tumors cell. Adapted from (Thamilselvan.S et al., 2024)

Histological grade	Percentage of undifferentiated cells
Well-differentiated (Grade I)	<25% undifferentiated cells
Moderately differentiated (Grade II)	<50% undifferentiated cells
Poorly differentiated (Grade III)	<75% undifferentiated cells
Anaplastic/pleomorphic (Grade IV)	>75% undifferentiated cells

Bryne's grading system evaluates four aspects of the tumor's deep invasive margin: the degree of keratinization, nuclear polymorphism, the pattern of invasion, and lymphoplasmacytic infiltration (Table 8) (Walker.M et al., 2003).

This system focuses on examining tumor cells in the deepest part of the tumor, which are less differentiated and interact with the patient's immune system. It offers several advantages, including its applicability to incisional biopsies and its superior prognostic value compared to other grading systems (Thamilselvan.S et al., 2024).

*Table 8. Bryne's histological grading system along with its scoring (1982). The tumor cells are graded at the invasive tumor front. Adapted from (Thamilselvan.S et al; 2024). *: not including for grading*

Morphological feature	Score			
	1	2	3	4
Degrees of keratinization	Highly keratinized (>50% of the cells)	Moderately keratinized (20–50% of the cells)	Minimal keratinization (5–20% of the cells)	No keratinization (0–5% of the cells)
Nuclear polymorphism	Little nuclear polymorphism (>75% mature cells)	Moderately abundant nuclear polymorphism (50–75% mature cells)	Abundant nuclear polymorphism (25–50% mature cells)	Extreme nuclear polymorphism (0–25% mature cells)
Number of mitoses per 10 high-power fields*	0–1	2–3	4–5	>5
Pattern of invasion	Pushing, well-delineated, infiltrating borders	Infiltrating, solid cords, bands, and/or strands	Small groups or cords of infiltrating cells (>15)	Marked and widespread cellular dissociation in small groups and/or in single cells (<15)
Lymphoplasmacytic infiltration	Marked	Moderate	Slight	None
Final Score: Grade I (well differentiated): 4–8; Grade II: 9–12 (moderately differentiated); Grade III: 13–16 (poorly differentiated)				

1.3.Diagnostic

A rapid and early diagnosis of OC, which can improve its prognosis, and allow the application of more conservative treatment modalities over a shorter period of time is imperative (Zargaran.M., 2014). However, although the oral cavity is easily accessible for palpation exams, early-stage OSCC is hard to detect because the lesion may not be palpable, and its color may resemble the surrounding mucosa. As a result, it is, in most cases, diagnosed after the first symptoms, indicating an advanced stage of the disease. Indeed, nearly two-thirds of OSCC cases are diagnosed at stage III or IV, signifying spread to adjacent tissues and regional lymph nodes (Chhabra.N et al., 2015).

Nonetheless, to improve diagnostic accuracy, techniques have been developed to complement clinical examinations, with biopsy considered the gold standard (Rosebuch.M et al.,2010).

The term "biopsy" was coined by French dermatologist Henry Ernst in 1879 (Vyas.T., 2018) and combines two Greek words: "*bios,*" meaning "life," and "*opsis,*"

meaning “vision.” A biopsy involves the excision of tissue for microscopic examination in order to establish a diagnosis (Zargaran.M., 2014).

Biopsies are not only indicated for diagnosing malignant tumors but should also be performed in the following situations (Zargaran.M., 2014).

- Lip and oral lesions that do not originate from local irritative factors such as trauma or inflammation.
- Lesions that persist for more than two weeks after eliminating local irritants.
- Lesions suspected of malignancy
- And many others such as autoimmune pathology

There are no absolute contraindications, but some facts require special attention such as:

- Normal anatomic and racial variations such as physiologic pigmentation, leukoedema, linea alba, tori, exostoses, and others.
- Compromised general health of the patient or a history of diathesis, including patients on anticoagulant therapy.
- Proximity of lesions to vital anatomic vascular, neural, or ductal structures, as well as lesions in areas of difficult surgical access.
- Immediate pre- or post-radiation therapy. (Vyas.T., 2018).

There are different types and techniques of biopsy depending on several factors. The technique is also divided into two groups: incisional and excisional biopsies (Zargaran.M., 2014).

Incisional biopsy, considered the gold standard, involves the excision of part of the lesion along with a portion of healthy tissue. This technique is used when it is not possible to remove the entire lesion, such as with lesions larger than 1 cm in diameter (Rosebuch.M et al., 2010).

Excisional biopsy involves removing the entire lesion along with healthy tissue as a safety margin (2–3 mm). This is used for lesions smaller than 1 cm in diameter, which are likely to be benign (Vyas.T., 2018).

In addition, other mechanisms can be useful.

Punch biopsy: This can be either an incisional or excisional technique that involves passing the punch through the keratinized surface down to the basal layer of the epithelium. It is a quick, and simple procedure, which is a significant advantage for both the practitioner and the patient. The goal is to capture the deepest epithelial cells (Chhabra.N et al., 2014). However, it is important to mention that this technique is limited to the superficial part of the epidermis and mesenchyme, and its use is discouraged in areas rich in vascular or neural plexuses (Zargaran.M., 2014) (Figure 3).

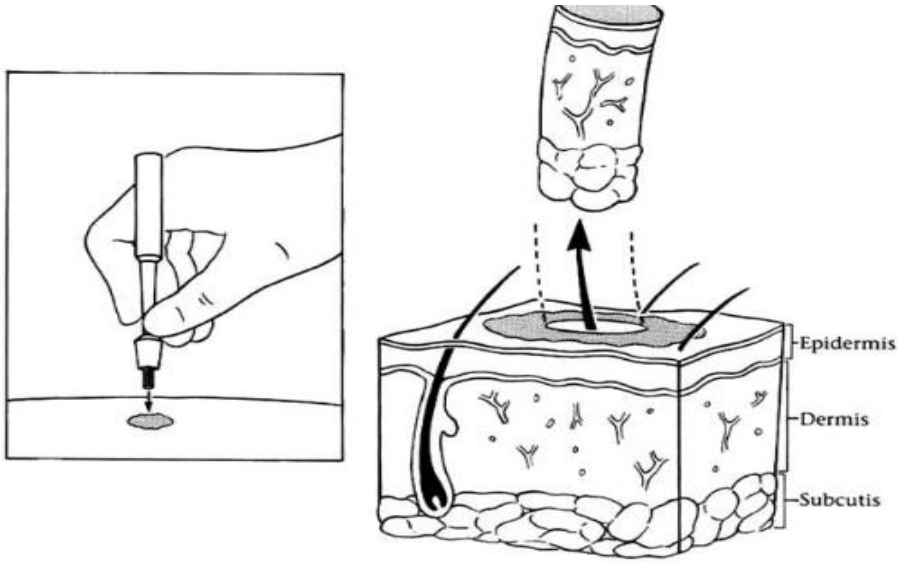


Figure 3. Punch biopsy. Adaptated from(Vyas.T; 2017)

In recent times, new non-invasive adjunct techniques have emerged to facilitate the detection of abnormalities in the mucosa. The diagnosis is then confirmed by histological examination. (Vashisht.N et al., 2014)

Among these techniques, we can find:

Autofluorescence, a technique based on a number of fluorophores sensitive to the morphological and biochemical alterations associated with neoplasia, enables us to distinguish healthy tissue from neoplastic tissue by means of the different fluorescence signals emitted in the tissue at different wavelengths (400-460nm) (Lima.I et al., 2021). The *VELscope*® is a portable device designed to facilitate visualization of the oral cavity by exciting endogenous fluorophores such as collagen, elastin, keratin, flavin adenine dinucleotide (FAD), and reduced nicotinamide adenine dinucleotide (NADH). In the presence of cellular alterations, changes in fluorophore concentrations occur, leading to variations in light absorption and diffusion within the tissue. Abnormal tissues appear dark brown to black due to reduced fluorescence levels, while healthy tissues emit a pale green autofluorescence (Shin.D et al., 2010). This method proves highly effective for obtaining information on cell morphology, behavior, and energy metabolism, enabling the distinction between normal and neoplastic tissues (dos Santos.L et al., 2022) (Figure 4).

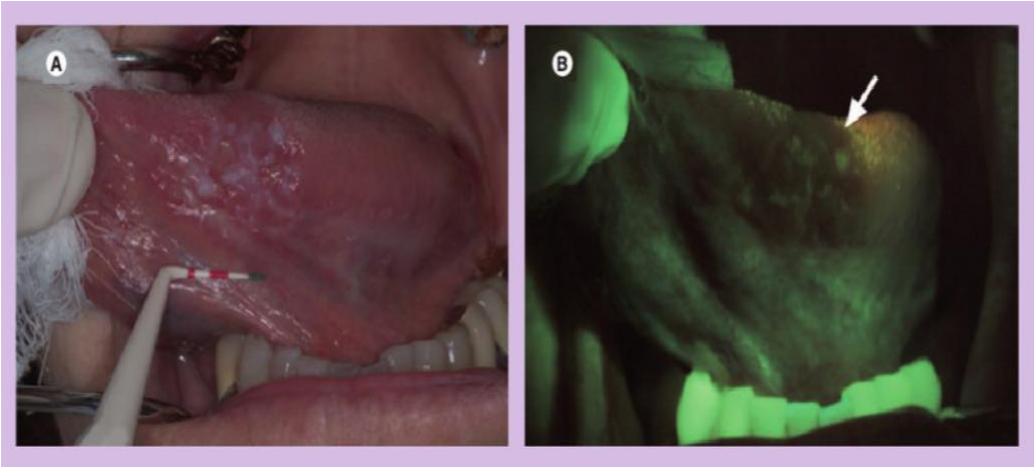


Figure 4. Wide-field autofluorescence imaging (Shin et al; 2011)

Chemiluminescence refers to light emission with limited heat production as a result of a chemical reaction. Various colors are produced, including blue, green, yellow-green, yellow, orange, and red. Several chemiluminescence systems exist, with luminol and peroxyoxalate being the most widely used (Vashisht.N et al., 2014). This technique relies on the ability of acetic acid to enhance keratinized surface areas, rendering keratin more visible to the naked eye. A subtle leukoplakia that might initially go unnoticed can be

detected within just one minute of contact with acetic acid (Chhabra.N et al., 2014). The *ViziLite*®, a commercially available device, uses blue light to illuminate tissues and detect abnormalities. However, it is worth noting that optimal results require using this technique in complete darkness, which may be challenging in modern dental offices.
Initial studies by Epstein et al. and Kerr et al. suggested that this device could potentially aid in detecting premalignant lesions by enhancing brightness and clarity (Shin.D et al., 2010) (Figure 5).

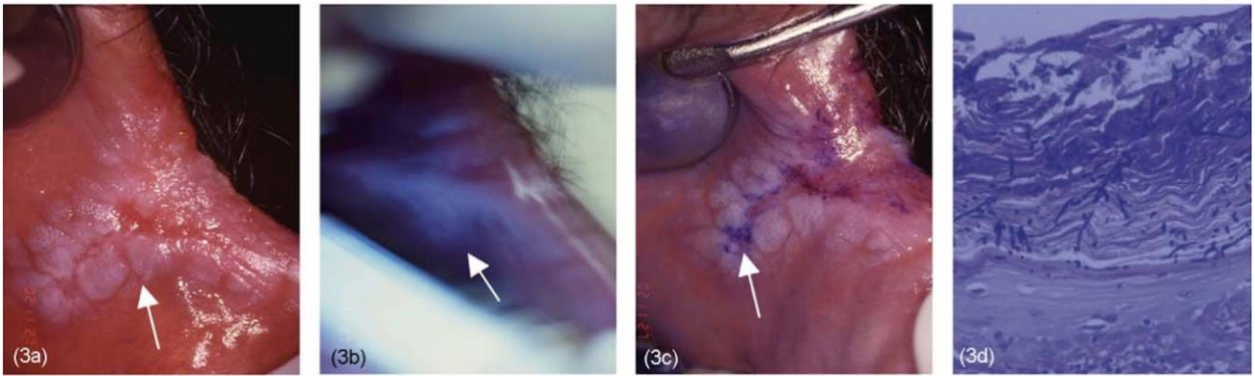


Figure 5a. Clinically identified leukoplakia left coommisure. Figure 5b. Vizilite 1 positive. Figure 5c. Tolonium chloride negative. Figure 5d. histologically chronic hyperplastic candidiasis (X200). (Ram, Siar; 2005)

Toluidine blue, also known as tolonium chloride, was discovered by William Henry Perkin in 1856 and has since been used in various medical fields. This metachromatic dye selectively stains acidic tissue components such as sulfates, carboxylates, and phosphate radicals (DNA, RNA), enabling early detection of nuclear changes indicative of malignancy (Vijayakumar.V et al., 2019). The use of this technique offers several advantages, including being quick and cost-effective. Additionally, it provides information about lesion margins, aiding dental surgeons in biopsy selection. Although some drawbacks, such as the risk of false positives, are worth noting, toluidine blue demonstrates high sensitivity, with reported values ranging from 84% to 100% (Chhabra.N et al., 2014) (Figure 6 and 7).

The adoption of these new methods has increased the potential for earlier identification and appropriate treatment, ultimately aiming to improve survival rates and quality of life (Rini et al., 2019).

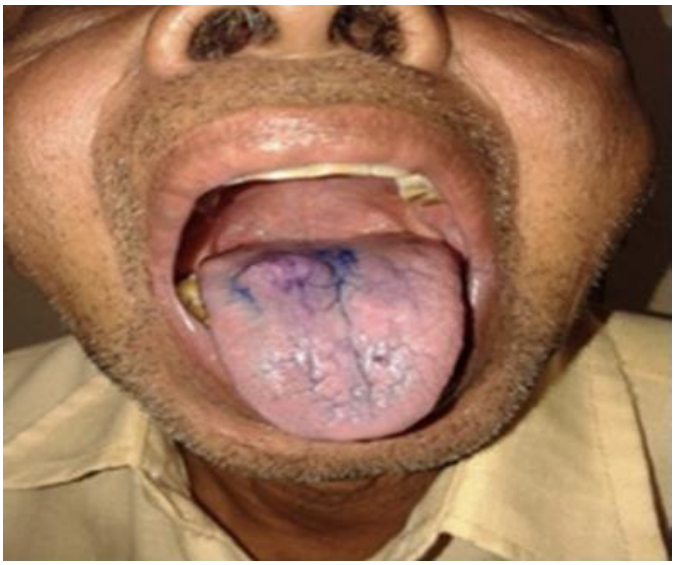


Figure 6. Benign lesion after toluidine blue staining (Vijayakumar.V et al., 2015)

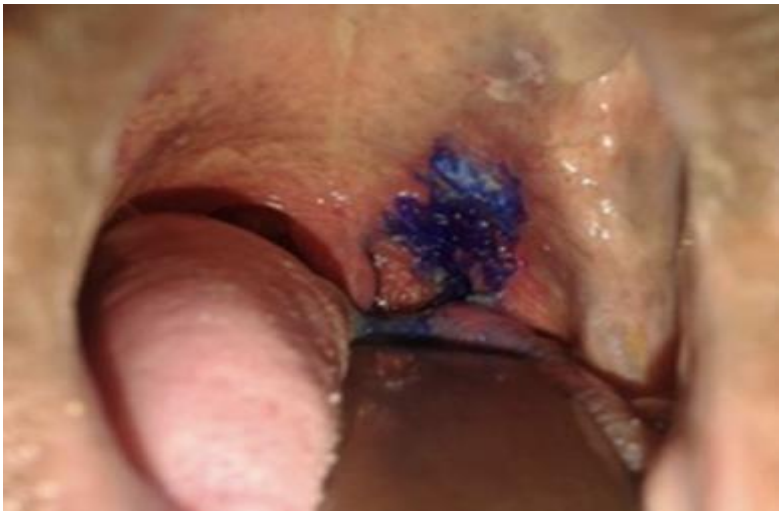


Figure 7. Malignant lesion after toluidine blue staining (Vijayakumar.V et al., 2015)

Various methods are available to diagnose oncogenic HPV infection.

It is possible to detect HPV using ADN, mARN or levels proteins. For DNA, methods are by polymerase chain reaction (PCR) or by in situ hybridization (ISH). These methods help identify the oncogenic role of HPV in OSCC and OPSCC.

Quantitative PCR (qPCR) can be used in order to detect the quantity of high-risk HPV DNA and reflect their oncogenic role. (Yakin et al., 2019).

PCR and ISH tests can also indicate the presence or absence of E6/E7 mARN and ISH is considered the gold standard for HPV-OPSCC. (Yakin et al., 2019).

P16 immunohistochemistry also plays an important role in the detection of E6/E7 mRNA in tissues and allows the detection of p16 tumor suppressor protein expression, a marker of high-risk HPV infection (Yakin et al., 2019).

1.4. Treatment

Several types of treatment are available for cancers of the oral cavity and oropharynx. A discussion between practitioner and patient is essential to determine the best possible options. It's important to notify that the type of treatment performed will depend on many factors, such as the type and stage of the cancer. A stage 1 cancer and a stage 3 cancer should not be treated in the same way (Rini et al., 2019).

The most common treatments are surgery, radiotherapy and CT. A combination of treatments is possible in order to optimize results (Liu.C et al., 2022).

Surgery is the most common treatment for OC. Techniques vary according to the extent of the lesion and the stage of the disease. It may be used alone or in combination with radiotherapy.

Surgery alone is recommended for early stages (stage 1/2), with no extension to lymph nodes (N0) and no metastases (M0) (Deng et al., 2011).

Lymph node removal (neck dissection) can sometimes be part of the treatment plan. There are two distinct methods of lymph node removal. The first one is to remove healthy lymph nodes at the same time as the tumor (elective neck dissection). The second one is a more conservative approach, removing lymph nodes only when they become cancerous (Worthington.H et al., 2023).

In addition to surgery, radiotherapy can be applied after surgical treatment. A large primary tumour and signs of perineural, lymphatic and vascular invasion are factors that may necessitate radiotherapy. Doses vary from person to person but are generally 60 Gray (Gy) divided into 30 fractions of 2Gy over a 6-week period.

This combination of treatments has proved favorable for slightly more advanced cancers (Deng et al., 2011).

Radiotherapy can also be used on its own, as is usually the case when treating oropharyngeal cancer (Johnson.D et al., 2021).

CT is the use of a drug to kill or inhibit the growth of a cancer cell; it can be used with or without radiotherapy. (Chamoli.A et al., 2021).
These drugs are cytostatic and cytotoxic, and by damaging DNA will kill cancer cells.
The chemotherapeutic drugs approved for OC are Cisplatin, carboplatin, 5-Fluorouracil, bleomycin, docetaxel, hydroxyurea, methotrexate (Chamoli.A et al., 2021).
Definitive treatment with CRT without upstream surgery is recommended for patients with advanced disease. (Chamoli.A et al., 2021).

Immunotherapy can be used in addition to the other options. We can use monoclonal antibodies, such as Cetuximab and Nimotuzumab; immune checkpoint inhibitors with Pemrbolizumab and Nivolumab (Silva.J et al., 2023).

It is important that the treatment plan is designed to achieve the most curative approach possible, although preservation of function remains the most important. To guarantee the most favorable outcome, a multidisciplinary team is essential (Montero.P., 2015).

1.5. Etiological factors

Several factors influence the development of cancers, particularly OSCC and OPSCC. Most of them are genetic and epigenetic factors such as alcohol and tobacco consumption, diet and nutrition, mate and the use of mouthwash. Poor oral hygiene can also have an impact on the oral cavity, while sexual behaviors and HPV play a role in the development of oropharyngeal cancer. (Kumar.M., 2016)

1.5.1. Tobacco

Tobacco, consumed predominantly by young and middle-aged adults, is known to be the most important risk factor for premature death (Chaturvedi.P et al., 2019).
Tobacco consumption is also known to be the main risk factor for developing OSCC as, in fact, tobacco is considered the cause of one-third oral cavity cancer. More than sixty

carcinogenic substances are contained in tobacco, one-quarter of which are carcinogenic to humans. Polycyclic aromatic hydrocarbons (PAHs) and N-nitrosamines (TSNAs) are the most serious (Ghantous.Y et al., 2018).

All these substances act according to different mechanisms such as oxidative stress in tissues, persistent reactive oxygen species (ROS), lipids, carbohydrates and DNA to disrupt cell cycle-regulated mutations or by affecting the immune system (Jiang.X et al., 2019).

Many studies have shown that risks increase with the number of cigarettes smoked per day and decrease proportionally with the length of time you stop smoking.

Besides, it has been demonstrated that smokers already diagnosed with OSCC have a higher probability of recurrence (Nokovitch.L et al., 2023).

In addition to tobacco consumption, smokeless tobacco (SLT) has become a widespread technique, particularly in South Asia. Although the majority of users believe that SLT is safer than tobacco consumption, it has been shown that there is a real link between SLT consumption and the development of oral cavity cancers. (Muthukrishnan.A., 2018)

The International Agency on Research for Cancer (IARC) has confirmed that SLT is carcinogenic for humans, particularly in the oral cavity, where it is applied directly (Muthukrishnan.A et Warnakulasuriya.S., 2018). In fact, the composition of SLT contains a whole complex of carcinogenic agents found in tobacco, such as TSNAs, PAHs, heavy metals like nickel and radioactive polonium-210. All these substances induce DNA damage, promote cell proliferation and inhibit apoptosis, leading to the development and proliferation of cancerous lesions in the oral cavity (Noor.A, Ramanarayana.B., 2024).

1.5.2. Alcohol

Alcohol is a known risk factor in the development of disease, particularly cancer. It is known to be a dose-dependent carcinogen caused via metabolic products resulting from the oxidation of ethanol to acetaldehyde by the alcohol dehydrogenase enzyme. Subsequently, this interaction between the results of metabolic products and DNA will cause mutations that could result in cancer (Badwelan.M et al; 2023). Some studies have reported acetaldehyde to be the most important carcinogen, but alcohol toxicity comes

from both products, directly from ethanol and indirectly from its metabolic product, which includes the ROS produced during its biotransformation involving CYP2E1.
In addition to these two components, alcoholic beverages contain several other substances derived from fermentation, such as ethyl carbamate (Ferraguti.G et al., 2022).

Several studies have shown that alcohol consumption combined with tobacco consumption considerably increases the risk of developing OC.
Indeed, this synergistic effect stems from the addition of the different carcinogenic mechanisms of alcohol and tobacco plus their ability to potentiate their respective toxic effects (Kondru.V., 2014).

1.5.3. Diet and nutrition

Nutrition is a crucial factor to consider when it comes to health and has been shown to be linked to the risk of developing cancer. Pro-inflammatory foods are known to heighten the risk of developing OC. In fact, these foods produce biomarkers such as C-reactive protein (CRP), interleukins (IL), notably IL-6, and homocysteine, which are associated with an increased risk of cancer. These include red meat, which, in addition to its pro-inflammatory composition, contains components such as nitrites and nitrates, which are unhealthy and can contribute to the formation of cancer cells. This is also the case for fried foods and foods with a high glycemic index, such as sodas and refined sugar, found in cakes, for example. Once consumed, these high-glycemic foods cause a drastic rise in blood sugar levels, which in turn leads to a significant rise in insulin levels, a hormone linked to tumor proliferation (Rodríguez-Molinero.J et al., 2021). Studies have also shown a link between the consumption of very hot tea and very spicy food and the risk of developing OC (Kijowska.J et al., 2024).

On the other hand, a diet rich in antioxidants, anti-inflammatories and anti-carcinogens reduces the risk of cancer. This is known as a protective diet. Protective foods include fiber- and vitamin-rich fruits and vegetables, olive oil and whole grains. (Hua.R et al., 2020)
The vitamin C contained in fruits such as citrus fruits has been shown to reduce the risk of developing a first cancer. Red fruits are known for their high concentration of

antioxidants. Vegetables contain high levels of vitamins and micronutrients such as beta-carotene, which protect against DNA damage (Hua.R et al., 2020).
Curcumin is also well known for its strong anti-inflammatory and restorative properties. (Imran.M et al., 2017)
Consumption of yellow vegetables such as beta-carotene-containing vegetables (carrots, pumpkin, sweet potato), cauliflower and fruit more than once a week has been shown to significantly reduce the risk of developing oral cavity cancers. (Gupta.B et al., 2017)

1.5.4. Mate

Maté is a tea native to South America, specifically Paraguay, Argentina, Uruguay and southern Brazil. It is usually drunk hot or very hot through an iron straw. Although mate is known for its antioxidant, hepatoprotective properties, and its many minerals such as iron, calcium and vitamins C, B1 and B2, it is considered a human carcinogen. This consideration is partly due to the very hot consumption of this tea, which can cause tissue burns. Mate also contains potential carcinogens, such as PAHs. A study has shown that at least 15 PAH components are found in different mate varieties (Dasanayake.A et al., 2009). Among these PAHs, phenanthrene and benzopyrene are present in both hot and cold mate (Deneo-Pellegrini.H et al., 2012). After several studies, an IARS research group hypothesized that the phenolic compounds already present in mate act as cancer promoters. In addition, tannins and N-nitroso compounds, which are carcinogenic compounds, have been found in this beverage.

A study by Oreggia et al. showed that mate drinkers had a 2.5-fold increased risk of developing tongue cancer. (Oreggia.F., 1991)

Stefani et al, found that exposure to mate increased the risk of developing oropharyngeal cancer by a factor of five. Finally, a two-fold increase in the risk of developing cancer was observed in individuals drinking very hot mate compared to those drinking it at moderate temperatures (De Stefani.E., 1988)

1.5.5. Areca nut

The areca nut is the endosperm of the areca fruit/drupe and comes from the regions of South Asia and part of East Africa. It can be eaten in a variety of ways: fresh, dried, roasted or sun-dried.

Areca nut is the first component of betel quid, which is now consumed by over 600 million people worldwide. Since 2004, IARC has classified areca nut as a Group 1 human carcinogen (Chen.W., 2022). This ranking is due to the composition of these nuts, which contain numerous alkaloids (0.15-0.67%), polyphenols (11-26%), fat (1.3-17%), saccharides (24-47%) and traces of tannins. Among the alkaloids, arecoline is the main component, and studies have shown its carcinogenicity and addictiveness (Senevirathnna.K et al., 2023). Arecoline is a psychoactive substance that stimulates the central nervous system by crossing the blood-brain barrier. Its main pharmacological effects are euphoria, tremors and bradycardia. Physiologically, however, areca chewing induces a feeling of well-being, increases salivation and body temperature, leading to a state of dependence and addiction (Li.WC et al., 2014).

Several studies have found that arecoline increases the incidence of tumors, particularly in the oral cavity. In addition, its reaction with sodium nitrite leads to the formation of N-nitrosamine, a known carcinogenic component (Chuang.HC et al., 2022). In addition to increasing the risk of OSCC, swallowing the juice when chewing areca causes direct contact of this substance with the oropharynx which also elevates the risk of developing OPSCC (Li.WC et al., 2014).

1.5.6. HPV and sexual behaviour

First discovered in skin cells around 1950, HPV is now well known and has become a risk factor in the development of SCC and, more specifically, OPSCC. Two types of OPSCC are classified according to HPV status: HPV-negative OPSCC, whose carcinoma is generally caused by tobacco and alcohol consumption. For HPV-positive OPSCC, cancer develops due to exposure to high-risk HPV especially during oral sex (Pytynia.K et al., 2014).

More than 200 virus subtypes are known, and HPV has been divided into two groups, the high risk (hr) and low-risk (lr) groups. Exposure to low-risk HPV will result in a lesion, but it will be a benign one, as is the case with exposure to subtypes 6 and 11. Exposure to hr HPV, on the other hand, dramatically increases the risk of developing cancer, as in the case of subtype 16, which is found in over 80% of HPV-positive cases, as well as for subtype 18. The malignancy caused by persistent infection is driven by oncoproteins E6 and E7, which are the main drivers of tumorigenesis by inactivating two of the most important tumor suppressors, pRb and p53 (Hübbers.C and Akgül.B., 2015).
Studies have revealed that HPV is more prevalent in men than in women, affects a younger population, and that the epithelial cells of the tonsillar crypts and the base of the tongue are the anatomical regions most affected. (Candotto et al., 2017).
This increase in the prevalence of HPV-positive OPSCC can be explained by changes in sexual habits in younger generations, including sexual activity starting earlier and earlier, an increase in the number of sexual partners and oral sex (Candotto et al., 2017).

1.5.7. Socio economic factors

We know that early detection of OSCC is the best way to improve a patient's chances of survival and reduce morbidity. However, most patients delay diagnosis, and the cancer is generally detected at an advanced stage. There are several reasons for this, including socio-economic factors. This term refers to the social and economic position that influences an individual's position in society. An individual's socio-economic position is an indicator of various factors, including symptom perception, access to care and communication with healthcare professionals. As a result, people with higher socio-economic status are diagnosed at a much earlier stage than those with lower status (Olsen.M et al., 2015).

According to a study by Vidya K. Lohe et al., around 30% of patients wait around three months after the onset of symptoms before consulting a doctor. This delay is linked to socio-demographic, socio-economic, socio-educational, socio-cultural and socio-professional factors.

Smith et al concluded in their study that recent data showed that emotional determinants such as fear, patients' ignorance of recognizing potential symptoms and financial barriers explained this delay.

A study in Germany found associations between the risk of death from cancer and socio-economic factors such as gender, marital status and education levels. Men were found to be the most affected by cancer (66.8% vs. 33.2%). The main reason for this difference is that men are exposed to more risk factors, in particular tobacco and alcohol consumption, which is higher than in women. A link between level of education and incidence of OC was demonstrated in this study. More than three-quarters of patients did not have a university degree. In addition to the association between education level and disease incidence, there is also a correlation between education level and disease survival. A lack of knowledge in this area would explain this link. It also investigated patients' marital status, which was found to be related to tobacco and alcohol consumption, as well as tumor stage at diagnosis. This is because people who are married or in a relationship are less affected by tobacco and alcohol addictions, so they are less exposed to the main risk factors. What's more, most of these persons are diagnosed at an earlier stage than single people, which is probably due to the fact that in a relationship people take care of each other, and there is more motivation to consult a professional as soon as the first symptoms appear. (Muallah.D et al., 2022)

Links have been found between socio-economic factors and HPV-related tumors, particularly HPV-positive, the victims of which are predominantly people with a certain socio-economic status. HPV-negative tumors, correlated with tobacco consumption, are more common in patients with low socio-economic status. (Dahlstrom.K et al., 2015).

A study conducted by the International Head and Neck Cancer Epidemiology Consortium has reported that the number of sexual partners and the practice of oral sex increases with higher socio-economic status, particularly among men. Conversely, these situations are more observed in women with low socioeconomic status (Dahlstrom.K et al., 2015).

1.5.8. Mouthwash

Mouthwashes are known as liquid solutions of antiseptics used to reduce the bacterial load in the oral cavity. Alcohol is often added to mouthwashes at concentrations ranging from 5% to 27% for its antiseptic properties and as an activator for certain active ingredients such as mint and thymol. It is known to have carcinogenic effects on the oral cavity, either directly or via acetaldehyde. (Ustrell-Borràs.M et al., 2020)

It was Weaver et al in 1979 who suggested a potential interaction between mouthwash use and an increased risk of oral cavity cancer.
Although studies contradict each other as to whether this risk is increased, it has been proven that people who consume tobacco and alcohol have a high risk of developing cancer. This risk is even greater when the patient does not have good oral hygiene. In people with no other risk factors, many studies carried out show a weak link between the use of mouthwash and the development of cancer.

While there is not yet enough evidence to prove that mouthwash use alone increases the risk of developing oral cavity cancer, it has been established that mouthwash use significantly increases salivary levels of acetaldehyde, a known carcinogenic component from the very first minutes (Ustrell-Borràs.M et al., 2020), (Hostiuc.S et al., 2021).

1.5.9. Bad oral hygiene

Poor oral hygiene (POH) is considered a risk factor for the development of OSCC. Factors contributing to POH include irregular tooth brushing, irregular visits, low socio-economic status, and alcohol and tobacco consumption. (Mathur.R et al., 2018)

An Indian study showed that all patients with OSCC in this study visited a dentist less than once a year. Laprise et al found similar results in their study, with 93% of patients not visiting the dentist regularly. A link has also been made between the consumption of tobacco, areca nut, alcohol and a POH. Though these risk factors are independent, and POH is not a direct causative agent in carcinogenesis, it nevertheless catalyzes the problem by increasing the carcinogenicity of these carcinogens.

A German study by Maier et al. showed that chronic alcoholism caused neglect of oral hygiene, which in turn led to POH. Tobacco and areca nut consumption lead to a deterioration in oral hygiene, resulting in tooth loss, caries and periodontal disease. A POH is the main etiological factor for the development of periodontitis, which if it progresses will lead to tooth loss. Indeed, an association between chronic gingivitis and OSCC has been discovered. This is also the case for tooth loss as a consequence of periodontal disease.

Thus, regular check-ups are fundamental to maintaining satisfactory oral hygiene (Marques.L et al., 2008), (Mathur.R et al., 2018).

1.5.10. Genetic factors

Cancer is known as a multifactorial disease in which genetics are implicated. The disease is caused by an accumulation of changes in excitatory or inhibitory cellular pathways. According to some estimates, it takes between three and six mutations for a normal cell to become a malignant one (Jurel.S et al., 2014).

Genetic changes in the oral cavity are divided into two categories: dominant and recessive. In the case of dominant changes, proto-oncogenes and certain tumor suppressor genes will be affected by loss or gain of function. As for recessive changes, it is the growth inhibitory genes or tumor suppressor genes that will be affected by a loss or gain of function (Ali.J et al., 2017).

Specific mutations have been identified as being associated with an increased risk of OC. These include patients affected by Li-Fraumeni syndrome whose germline mutation is located in the TP53 gene, as well as patients with Fanconi anemia characterized by defects in the DNA repair process, resulting in chromosomal instability that can lead to very aggressive OCs at a relatively young age. Finally, congenital dyskeratosis patients with telomerase maintenance defects have a thousand-fold increased risk of developing OSCC (Li.CC et al., 2019).

1.6. Epidemiology

Prast, in 1995, gave a more recent definition of the term “epidemiology” and defined it as: “Epidemiology studies, in a given population, the distribution of different health states or health phenomena and their determinants. The results of this study are used to combat health problems”.
In the case of cancer, epidemiology focuses on malignant diseases (Silva.I., 1999).

1.6.1. Incidence

According to the WHO, incidence is “The number of new cases of cancer occurring in a defined population over a given period.” (GLOBOCAN).

1.6.2. Prevalence

According to the United States Cancer Statistics, prevalence is “The number of people with a specific disease or condition in a given population at a specific time. This measure includes both newly diagnosed and pre-existing cases of the disease.” (U.S. cancer Statistics).

1.6.3. Mortality

The mortality of a disease corresponds to the number of people who died from it during a given period. (Grosclaude.P, Fallu.B., 1998).

1.6.4. Survival

Cancer survival means the percentage of people still alive after a particular amount of time.
Statistics are usually written as: 1 year survival, 5 years survival, 10 years survival.

2. Objectives

The aim of this work is to collect data published in official databases, both by the European Union and the World Health Organization in order to study the oral cancer epidemiology. To this end, we will evaluate incidence, prevalence, mortality and survival rates in Portugal and France. Subsequently, a comparison will be made with different world regions such as Asia, The United-States and Europe.

2.1. The global cancer observatory

The global cancer observatory (GLOBOCAN) is a database of cancer statistics. This platform focuses on the visualization of cancer indicators using IARC including GLOBOCAN. Other indicators are used such as the incidence of cancer in the 5 continents or the international incidence of childhood cancer.
This database is the most reliable in the world.

2.2. The European cancer information system

The European Cancer Information System (ECIS) is a platform similar to GBO, which provides cancer epidemiological data for European countries.

3. Materials and methods

3.1. Outline

This is an observational, descriptive, retrospective and multicenter epidemiological study.

First of all, the Portuguese and the French population who are affected by OC taking into account numbers of 2022.

Second of all, we compared these numbers with 2010 data for both countries.

Finally, we compared these populations with official data from Asia, the USA and the rest of Europe, followed by an analysis of 5-year survival for all regions.

3.2. Inclusion criteria

All populations in Europe, Asia and the USA with OC between 2010 and 2022 were included.

4. Results

4.1.Descriptive analysis of incidence in Portugal

In 2022, according to GBO, the incidence of lip and oral cavity cancer in Portugal is 6.3 per 100 000 inhabitants of all sexes and ages (0-65+).
The incidence is 10.6 in men and 2.4 in women (per 100 000 inhabitants).
The incidence of oropharyngeal cancer is 3.0 in total, 6.0 in men and 0.35 in women (per 100 000 inhabitants) (Figure 8).

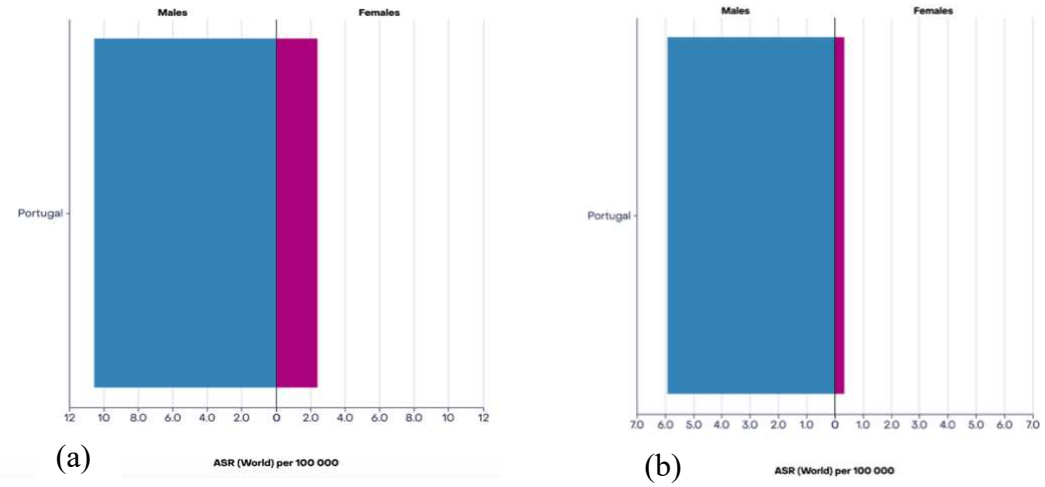


Figure 8a. Age- standardized rate (World) per 100 000, incidence, Males and Females, in 2022 for lip and oral cavity cancer in Portugal.
Figure 8b. Age-standardized rate (World) per 100 000, incidence, Males and Females, in 2022 for oropharyngeal cancer in Portugal
Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatory. Available at: https://gco.iarc.fr/today.

For more precise data, the population was divided into four distinct groups. The first one from ages 20 to 29, the second one from 30 to 44, the third one from 45 to 64 and finally a group whose population is over 65.

Thus, the incidence of lips and oral cavity cancer for the 20-29 age group is 0.93 in men and 0.37 in women. Overall, it is 0.65 (per 100 000 inhabitants).
However, no data is available on the incidence of oropharyngeal cancer in this age group.

In the population with lip and oral cavity cancer aged between 30 and 44, the incidence is 10.7 in men and 1.2 in women. The overall incidence is 5.8 (per 100 000 inhabitants).

For those with oropharyngeal cancer, the overall incidence is 1.7; 3.0 in men and 0.39 in women (per 100 000 inhabitants) (Figure 9).

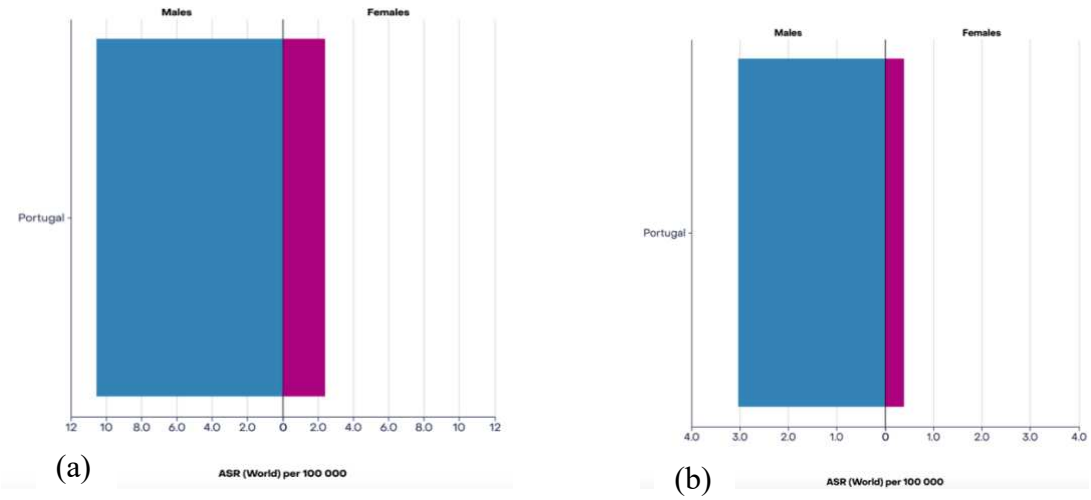


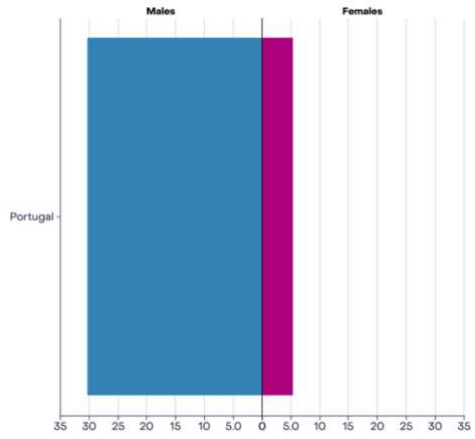
Figure 9a. Age-standardized rate (World) per 100 000, incidence, Males and Females, [30-44] in 2022 for lip and oral cavity cancer in Portugal

Figure 9b. Age-standardized rate (World) per 100 000, incidence, Males and Females, [30-44] in 2022 for oropharyngeal cancer in Portugal

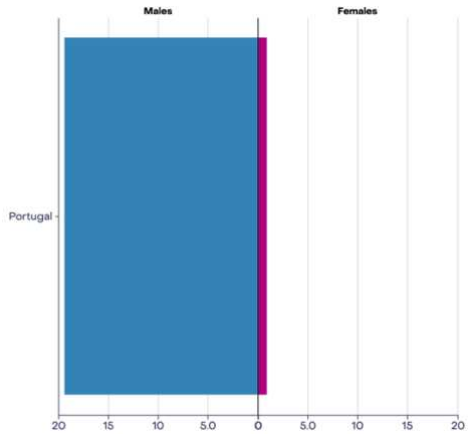
Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatory. Available at: https://gco.iarc.fr/today.

Between 45 and 64, the overall incidence for lip and oral cavity cancer is 17.2; 30.4 for men and 5.4 for women (per 100 000 inhabitants).

For oropharyngeal cancer, the overall incidence is 9.7, including 19.5 in men and 0.94 in women (per 100 000 inhabitants) (Figure 10).



(a)

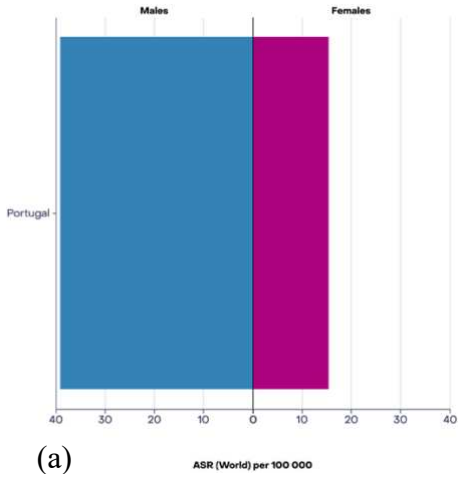


(b)

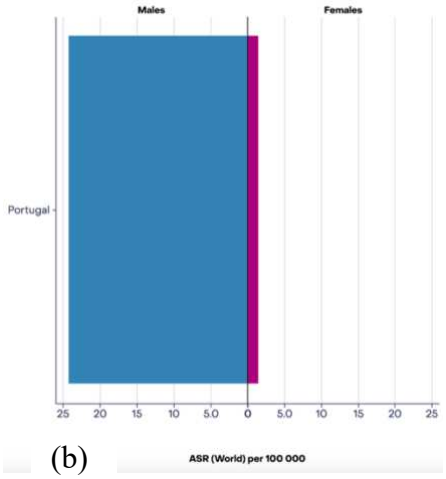
Figure 10a. Age-standardized rate (World) per 100 000, incidence, Males and Females, [45-64] in 2022 for lip and oral cavity cancer in Portugal
Figure 10b. Age-standardized rate (World) per 100 000, incidence, Males and Females, [45-64] in 2022 for oropharyngeal cancer in Portugal
Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatory. Available at: https://gco.iarc.fr/today.

In people over 65 with lips and oral cavity cancer, the overall incidence is 26.1; 39.2 in men and 15.4 in women (per 100 000 inhabitants).

For oropharyngeal cancer it is 11.7, 24.4 and 1.5 (per 100 000 inhabitants) respectively. (Figure 11).



(a)



(b)

Figure 11a. Age-Standardized Rate (World) per 100 000, Incidence, Males and Females, [65+] in 2022 for lip and oral cavity cancer in Portugal
Figure 11b. Age-Standardized Rate (World) per 100 000, Incidence, Males and Females, [65+] in 2022 for oropharyngeal cancer in Portugal
Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatory. Available at: https://gco.iarc.fr/today.

4.2.Descriptive analysis of prevalence in Portugal

Portugal is one of the countries with the highest prevalence of cancer cases, particularly lip and OC.
In fact, for the year 2022, the overall prevalence of cases of this cancer is 1055, of which 765 are men and 290 women.
During this year, 7 cases of cancer of the lips and oral cavity were reported in subjects aged between 20 and 29. Of these, 5 were men.
In the 30-44 age group, a total of 99 cases were recorded, 88 of them in men and 11 in women.
Of the 445 cases in the 45-64 age group, 369 were men, while only 76 were women.
Finally, 503 cases were reported in the over-65s, with 303 cases among men and 200 among women.

Just like the incidence rate, the number of recorded cases of lip and oral cavity cancer in Portugal in 2022 was higher among older individuals, particularly those over 45. Men were by far the most affected.

In the same year, 475 cases of oropharyngeal cancer were reported. Of these, 443 were men and 32 were women.
Unlike lip and oral cavity cancer, there were no cases in the 20-29 age group.
There were 32 cases in the 30-44 age group, 87.5% of whom were men.
258 cases were recorded in the 45 to 64 age group, with 244 cases in men and only 14 in women.
Among the over-65s, 171 of the 185 cases were men.

Despite the lack of data for younger populations, oropharyngeal cancer mainly affects men aged 45 to 64.

4.3.Descriptive analysis of mortality in Portugal

Mortality varies according to cancer type and age group.

Thus, for cancer of the lips and oral cavity in 2022, overall mortality is 1.8, with a mortality of 3.1 for men and 0.63 for women (per 100 000 inhabitants).

For oropharyngeal cancer, overall mortality is 1.3, with a mortality rate of 2.6 for men and 0.13 for women (per 100 000 inhabitants) (Figure 12).

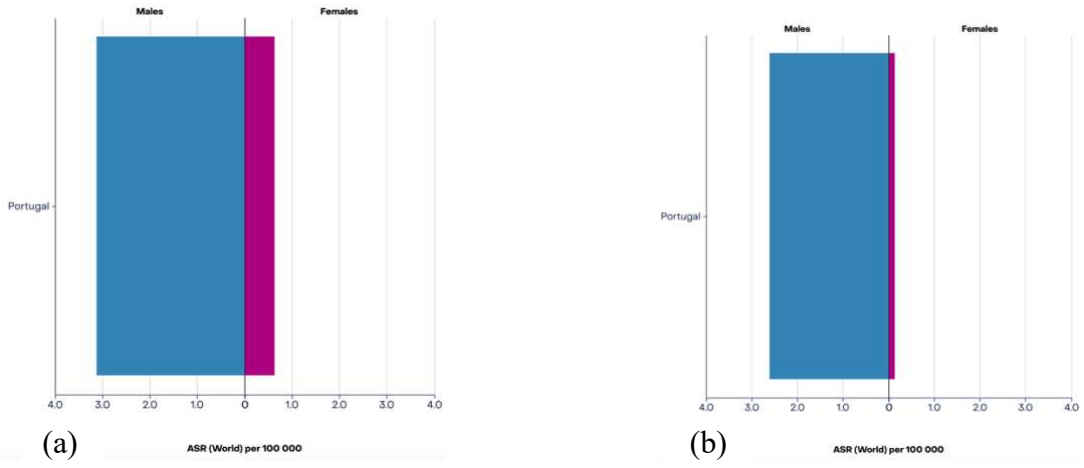


Figure 12a. Age-standardized rate (World) per 100 000, Mortality, Males and Females, in 2022 for lip and oral cavity cancer in Portugal
Figure 13b. Age-standardized rate (World) per 100 000, Mortality, Males and Females, in 2022 for oropharyngeal cancer in Portugal
Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatory. Available at: https://gco.iarc.fr/today.

No mortality data are available for young people aged 20 to 29.

Among subjects aged 30 to 44, the mortality rate for cancer of the lips and oral cavity is 0.98 overall; 1.9 in men and 0.09 in women (per 100 000 inhabitants).

For oropharyngeal cancer, the overall mortality rate is 0.33, of which 0.59 in men and 0.09 in women (per 100 000 inhabitants) (Figure 13).

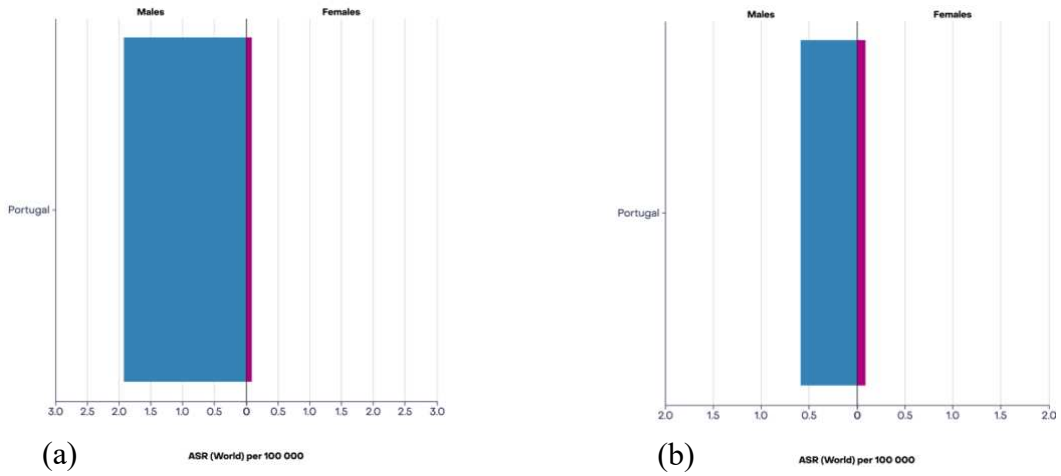


Figure 13a. Age-Standardized Rate (World) per 100 000, Mortality, Males and Females, [30-44] in 2022 for lip and oral cavity cancer in Portugal
Figure 13b. Age-Standardized Rate (World) per 100 000, Mortality, Males and Females, [30-44] in 2022 for oropharyngeal cancer in Portugal
Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatory. Available at: https://gco.iarc.fr/today

The 45-64 age group has an overall mortality rate for lip and oral cavity cancer of 5.2, with 9.4 for men and 1.3 for women (per 100 000 inhabitants).

For oropharyngeal cancer, the overall mortality rate is 4.3, with a rate of 8.7 in men and 0.36 in women (per 100 000 inhabitants) (Figure 14).

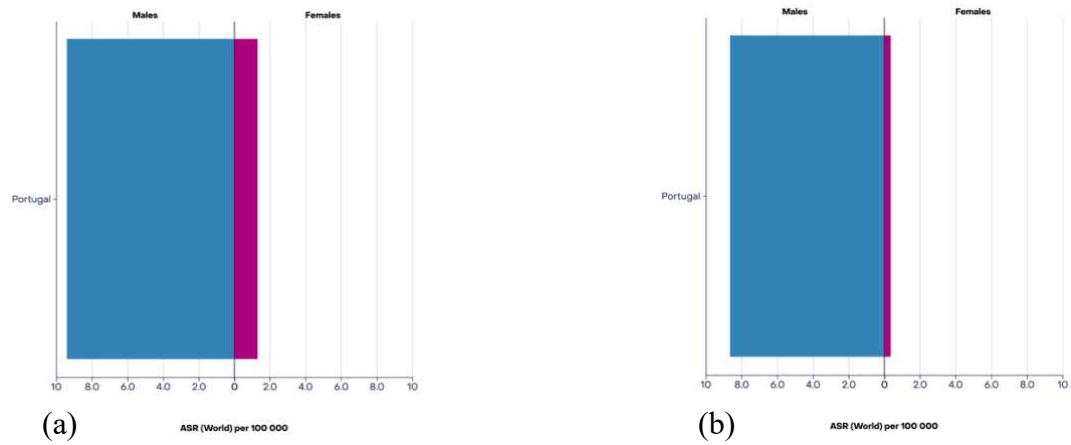


Figure 14a. . Age-Standardized Rate (World) per 100 000, Mortality, Males and Females, [45-64] in 2022 for lip and oral cavity cancer in Portugal
Figure 14b. Age-Standardized Rate (World) per 100 000, Mortality, Males and Females, [45-64] in 2022 for oropharyngeal cancer in Portugal
Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatory. Available at: https://gco.iarc.fr/today

In the over 65s, the overall rate is 9.2, with a rate of 14.4 in men and 5.1 in women for lips and oral cavity cancer (per 100 000 inhabitants).

Oropharyngeal cancer in this group has an overall mortality rate of 5.9, with a rate of 12.4 in men and 0.69 in women (per 100 000 inhabitants) (Figure 15)

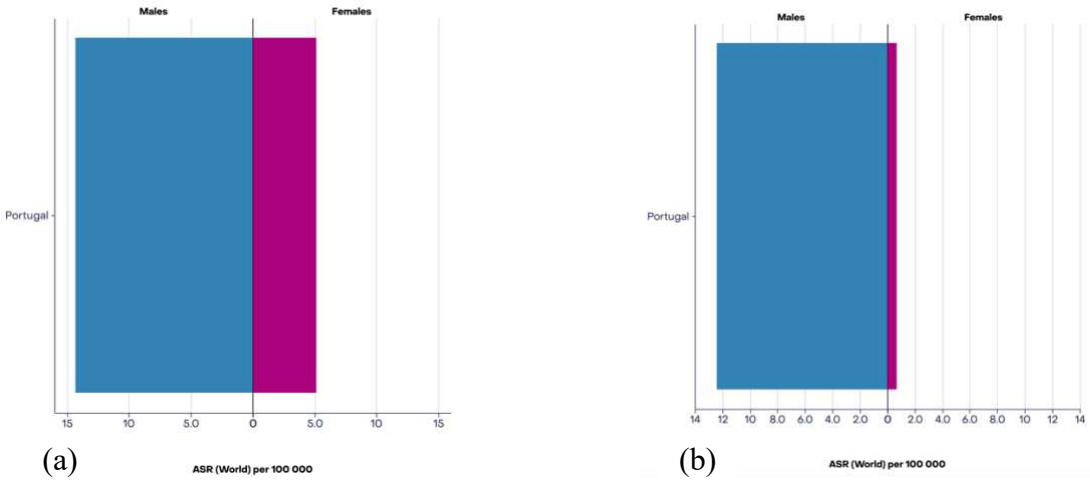


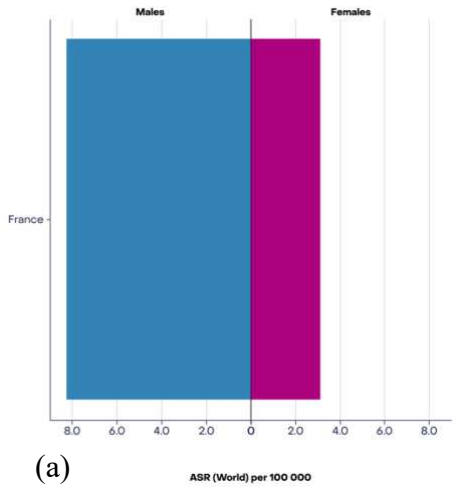
Figure 15a. Age-Standardized Rate (World) per 100 000, Mortality, Males and Females, [65+] in 2022 for lip and oral cavity cancer in Portugal
Figure 15b. Age-Standardized Rate (World) per 100 000, Mortality, Males and Females, [65+] in 2022 for oropharyngeal cancer in Portugal
Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatory. Available at: https://gco.iarc.fr/today

From all these data, it can be seen that the vast majority of mortality is among men, particularly in the over-65s. This high mortality rate applies to both types of cancers.

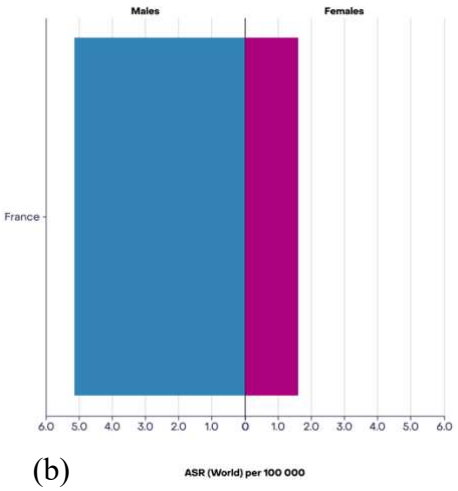
4.4. Descriptive analysis of incidence in France

France is a country known to have many cases of cancer each year.
In fact, according to GBO data for 2022, the overall incidence rate (age and sex combined) for cancer of the lips and oral cavity is 5.6, with a rate of 8.3 in men and 3.1 in women (per 100 000 inhabitants).

The rates for oropharyngeal cancer are 3.3, 5.2 and 1.6 (per 100 000 inhabitants) respectively. (Figure 16)



(a)



(b)

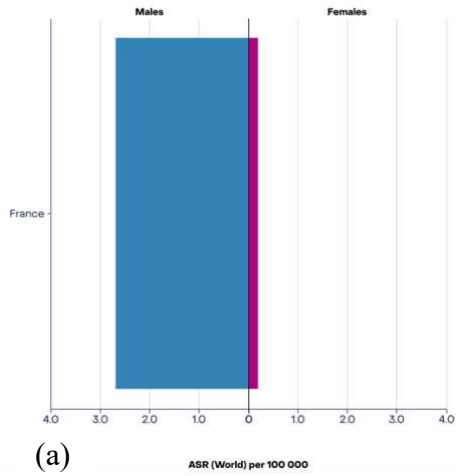
Figure 16a. Age-Standardized Rate (World) per 100 000, Incidence, Males and Females, in 2022 for lip and oral cavity cancer in France
Figure 16b. Age-Standardized Rate (World) per 100 000, Incidence, Males and Females, in 2022 oropharyngeal cancer in France
Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatoy. Available at: https://gco.iarc.fr/today

In younger age groups, the rate is relatively low, at 0.12 overall, with a rate of 0.19 for men and 0.05 for women (per 100 000 inhabitants).

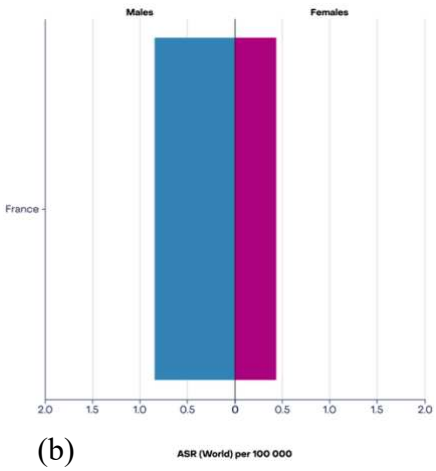
No data is available for oropharyngeal cancer.

Among people aged between 30 and 44, the overall incidence rate is 1.4. This rate is 2.7 for men and 0.20 for women (per 100 000 inhabitants).

For oropharyngeal cancer, the rates are 0.65, 0.85 and 0.44 (per 100 000 inhabitants) respectively. (Figure 17)



(a)



(b)

Figure 17a. Age-Standardized Rate (World) per 100 000, Incidence, Males and Females, [30-44] in 2022 for lip and oral cavity cancer in France
Figure 17b. Age-Standardized Rate (World) per 100 000, Incidence, Males and Females, [30-44] in 2022 for oropharyngeal cancer in France
Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatory. Available at: https://gco.iarc.fr/today

In the 45-64 age group, the overall incidence for lips and oral cavity cancer is 17.7. It is 26.7 in men and 9.1 in women (per 100 000 inhabitants).

In the case of oropharyngeal cancer, the overall incidence is 11.5; 17.9 in men and 5.5 in women (per 100 000 inhabitants) (Figure 18)

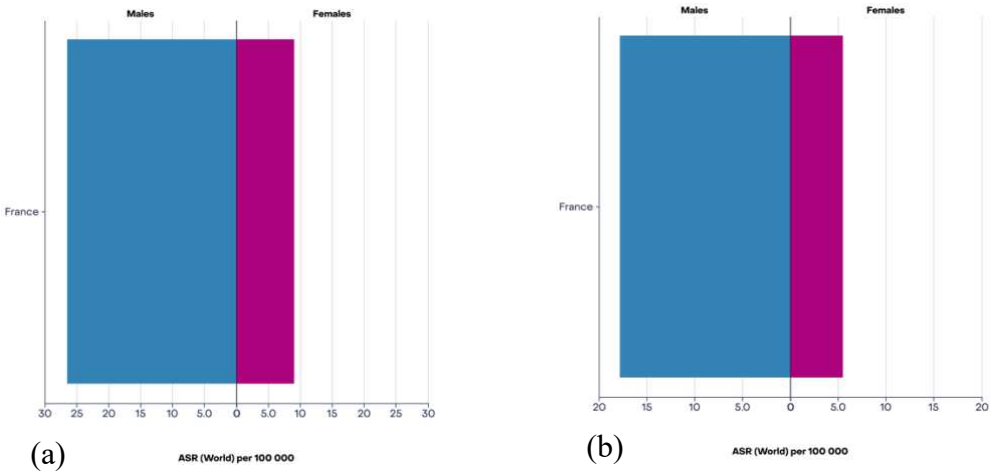


Figure 18a. Age-Standardized Rate (World) per 100 000, Incidence, Males and Females, [45-64] in 2022 for lip and oral cavity cancer in France
Figure 18b. Age-Standardized Rate (World) per 100 000, Incidence, Males and Females, [45-64] in 2022 for oropharyngeal cancer in France
Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatory. Available at: https://gco.iarc.fr/today

For the over 65s, the overall rate for lips and oral cavity cancer is 28. 38.4 for men and 19 for women (per 100 000 inhabitants).

For oropharyngeal cancer, the incidence rates are 14.3, 23.1 and 6.9 respectively (per 100 000 inhabitants). (Figure 19).

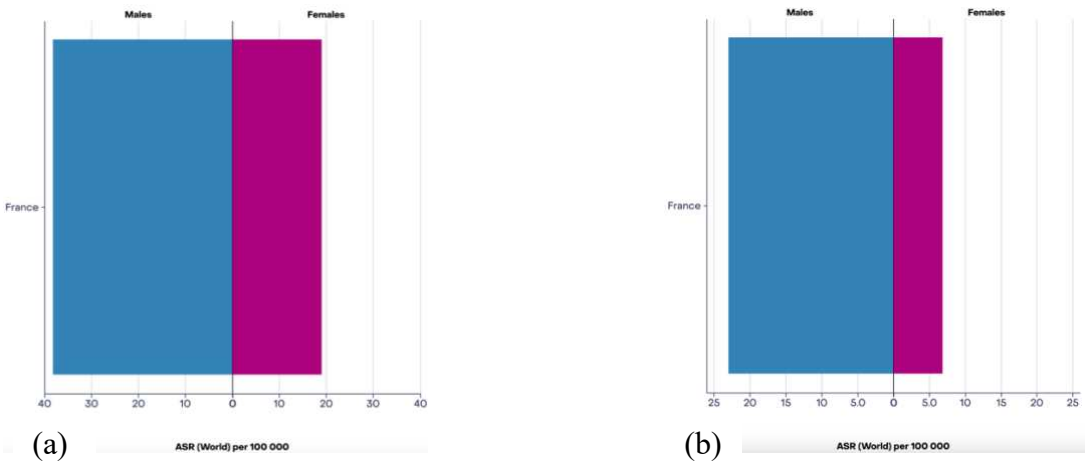


Figure 19a. Age-Standardized Rate (World) per 100 000, Incidence, Males and Females, [65+] in 2022 for lip and oral cavity cancer in France
Figure 19b. Age-Standardized Rate (World) per 100 000, Incidence, Males and Females, [65+] in 2022 for oropharyngeal cancer in France
Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatoy. Available at: https://gco.iarc.fr/today

As in Portugal, the incidence of these cancers is much higher in the population aged over 45, with a marked increase in the over-65s for cancer of the lips and oral cavity. Men are always the most affected. Although Portugal has fairly high rates, the data indicate even higher rates for France.

4.5. Descriptive analysis of prevalence in France

In 2022, data collected by the GBO made it possible to study the prevalence of cancer cases in mainland France. A total of 6 115 people were affected by lip and oral cavity cancer. Among those aged 20–29, only 9 cases were observed, including 7 men. In the 30–44 age group, 154 cases were recorded, with 144 being men. Among individuals aged 45–64, a total of 2782 cases were reported, including 2025 men and 757 women.
For those over 65, 3 165 cases were recorded, with 1 854 men and 1 311 women.

For oropharyngeal cancer, 3,342 cases were registered in 2022.
No data is available in the register for 20–29-year-olds.

There were 73 individuals affected by this cancer, including 47 men and 26 women in the 30-44 age group.
The 45-64 age group includes 1,899 cases, three quarters of whom are men.
The age group of individuals over 65 years old registered 1369 cases, 1020 of them men and 349 women.

Oropharyngeal cancer has a high prevalence in men over the age of 45, with an increase between the ages of 45 and 64.

4.6. Descriptive analysis of mortality in France

Overall mortality from cancer of the lips and oral cavity is 1.2 (per 100 000 inhabitants) for all ages and sexes combined.
For men it is 1.8 and for women 0.58 (per 100 000 inhabitants).

The overall mortality rate for oropharyngeal cancer is 0.90 (per 100 000 inhabitants) for both sexes and all ages.
For men it is 1.4 and for women 0.41 (per 100 000 inhabitants) (Figure 20).

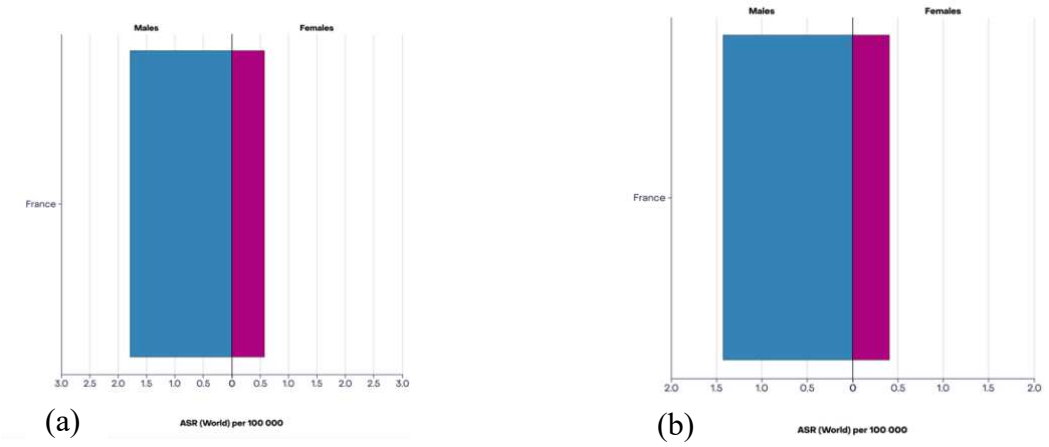
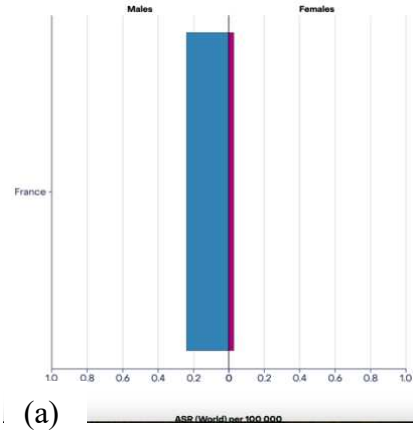


Figure 20a. Age-Standardized Rate (World) per 100 000, Mortality, Males and Females, in 2022 for lip and oral cavity cancer in France
Figure 20b. Age-Standardized Rate (World) per 100 000, Mortality, Males and Females, in 2022 for oropharyngeal cancer in France
Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatory. Available at: https://gco.iarc.fr/today

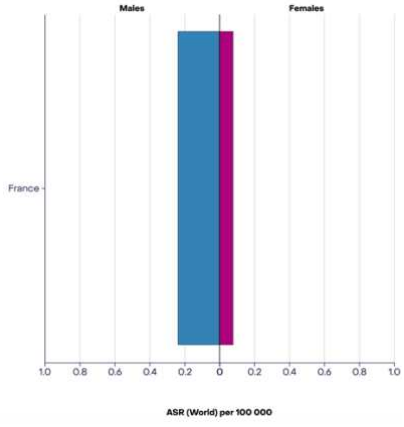
No registry data are available on the mortality rate of these cancers in young people aged 20 to 29.

For the population aged between 30 and 44, the overall mortality rate for lip and oral cavity cancer is 0.13, 0.24 for men and 0.03 for women (per 100 000 inhabitants).

For oropharyngeal cancer, the rates are 0.16, 0.24 and 0.08 (per 100 000 inhabitants) respectively. (Figure 21).



(a)



(b)

Figure 21a. Age-Standardized Rate (World) per 100 000, Mortality, Males and Females, [30-44] in 2022 for lip and oral cavity cancer in France
Figure 21b. Age-Standardized Rate (World) per 100 000, Mortality, Males and Females, [30-44] in 2022 for lip and oral cavity cancer in France
Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatory. Available at: https://gco.iarc.fr/today

This number rises to a total of 3.3 for lip and oral cavity cancer in the 45-64 age group, 5.3 in men and 1.4 in women (per 100 000 inhabitants).

In the case of oropharyngeal cancer, the figures are 2.9, 4.5 and 1.3 (per 100 000 inhabitants) respectively. (Figure 22).

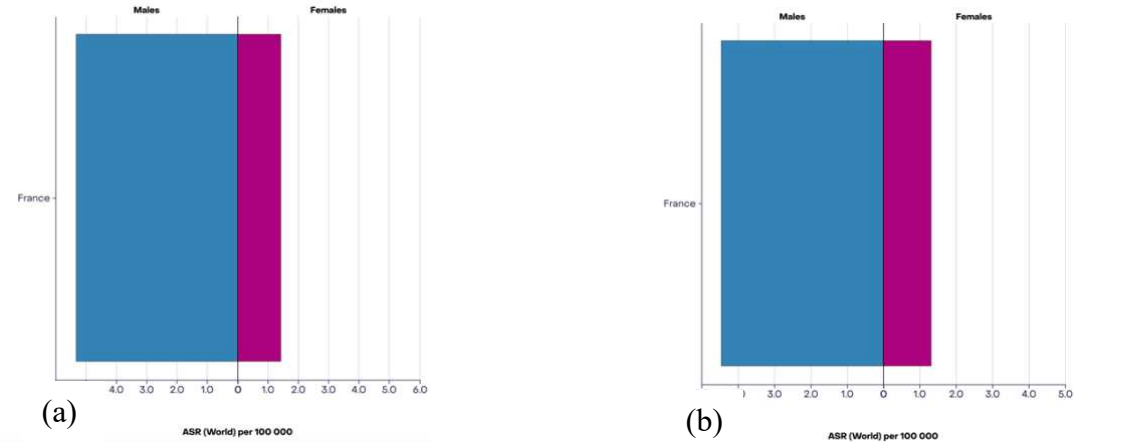


Figure 22a. Age-Standardized Rate (World) per 100 000, Mortality, Males and Females, [45-64] in 2022 for lip and oral cavity cancer in France
Figure 22b. Age-Standardized Rate (World) per 100 000, Mortality, Males and Females, [45-64] in 2022 for oropharyngeal cancer in France
Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatory. Available at: https://gco.iarc.fr/today

In the over-65s, the mortality rate rises drastically to 7.2 overall for lip and oral cavity cancer. This rises to 10.6 for men and 4.3 for women (per 100 000 inhabitants).

For oropharyngeal cancer, the rates are 4.6, 7.6 and 2.1 respectively (per 100 000 inhabitants) (Figure 23).

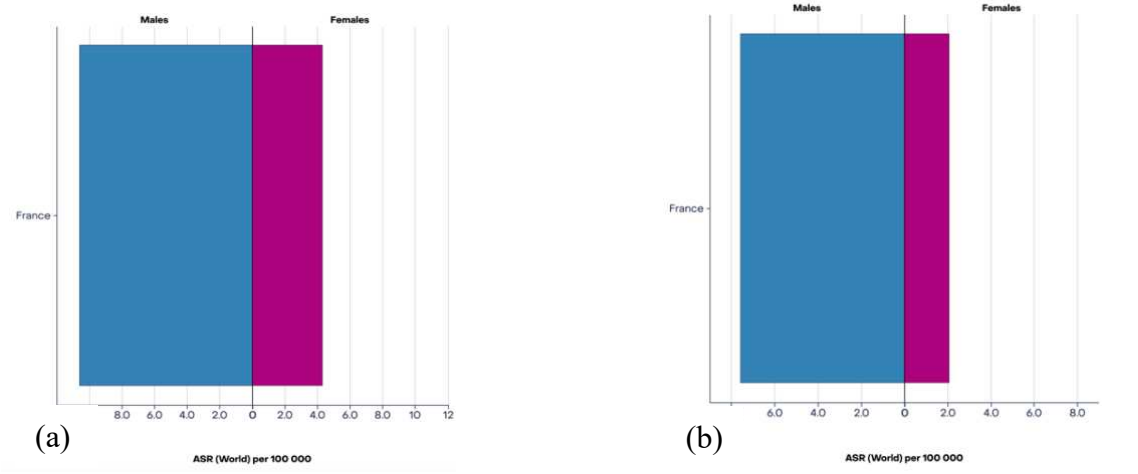


Figure 23a. Age-Standardized Rate (World) per 100 000, Mortality, Males and Females, [65+] in 2022 for lip and oral cavity cancer in France
Figure 23b. Age-Standardized Rate (World) per 100 000, Mortality, Males and Females, [65+] in 2022 for oropharyngeal cancer in France
Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatory. Available at: https://gco.iarc.fr/today

These data show that mortality is very high among men over 65, particularly for lip and OC.

4.7 Comparison of incidence and mortality (2010-2022)

In 2010, lip, oral cavity and oropharyngeal cancer were grouped into a single type.

Table 9. Comparison of lip, oral and oropharyngeal cancer incidence between Portugal and France, 2010-2022.

Country	Year	Gender	20-34 years	35-49 years	50-64 years	65+ years
Portugal	2010	Male	3.1	47.9	124.9	207.6
		Female	1.2	8	20.8	93.6
	2022	Male	2.3	24.4	55.5	63.6
		Female	0.46	2.7	7.4	16.9
France	2010	Male	1.35	59.5	283.2	388.7
		Female	2.73	16.7	51	107.7
	2022	Male	0.32	10.7	54.9	61.5
		Female	0.11	2.3	19	25.9

Men are the most affected, except in the 20-34 age group in France. In this age group, women have an incidence rate of 2.73, while men have a rate of 1.35 (per 100 000 inhabitants).

In 2010, Portugal had a lower incidence than France, except in the 20-34 age group, where Portuguese men had a higher incidence rate than French men (3.1/1.35) per 100 000 inhabitants.

In 2022, the trend is reversed, and up to the age of 50, Portuguese men have a relatively higher incidence rate than French men. Among women, incidence is similar between the two countries. For men over 50, Portuguese incidence is like French, but French women have higher rates than Portuguese women. (Table 9)

Table 10.Comparison of lip, oral and oropharyngeal cancer mortality between Portugal and France, 2010-2022.

Country	Year	Gender	20-34 years	35-49 years	50-64 years	65+ years
Portugal	2010	Male	0.3	16	52.7	108.7
		Female	0.6	2.2	3.8	35.3
	2022	Male	0.10	6.0	21.4	26.8
		Female		0.50	2.0	5.8
France	2010	Male	0.16	10.76	83.8	166.2
		Female	0.35	2.39	12.8	37.1
	2022	Male		2.0	12.2	18.2
		Female	0.01	0.52	3.4	6.4

In terms of mortality, there is a decline in both countries between 2010 and 2022. In 2010, mortality among the under-50s was higher in Portugal than in France, but the trend was reversed for the over-50s, with the French having a higher mortality rate than the Portuguese. Men are still the most affected.

For the year 2022, mortality rates among men are higher in Portugal. Although rates remain similar, French women have a higher mortality rate than Portuguese women. (Table 10)

4.8. Comparison of incidence and mortality in Portugal and in France with

4.8.1. Europe

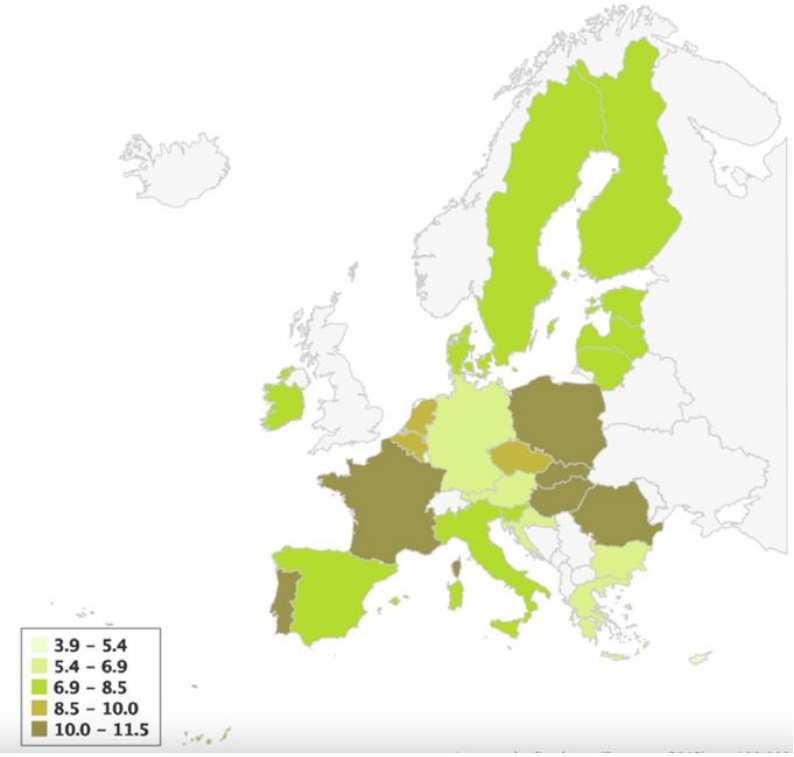


Figure 24. Estimated incidence of lip and oral cavity cancer in Europe for both sexes and all ages in 2022
Data from the European Cancer Information System (ECIS). Rates are standardized on the European population (ESR, per 100 000 inhabitants). Source: European Commission, Joint Research Center (JRC). Available at: https://ecis.jrc.ec.europa.eu.

Europe is a continent which can be divided in four, Northern Europe, Eastern Europe, Western Europe and Southern Europe. The cancer's incidence remains high in this continent, particularly for lips and oral cavity cancer.

Concerning Eastern Europe, Slovakia is the country with the highest incidence, at 11,5 (per 100 000 inhabitants). It is followed by Hungary and Poland, with incidence rates of 11.2 and 11 (per 100 000 inhabitants) respectively. With an incidence rate that remains high but slightly lower than their neighboring countries, the Czech Republic and Austria have incidence rates ranging from 6.7 in Austria to 8.8 in the Czech Republic (per 100 000 inhabitants).

For Northern European countries, the incidence rate varies between 7.5 and 8.5 with higher rates in Finland and Lithuania, where the incidence is 8.4 (per 100 000 inhabitants).

They are followed by Latvia, Sweden, Denmark and Estonia with incidence rates of 7.8, 7.7 and 7.5 (per 100 000 inhabitants) respectively.

In Southern Europe, the country with the highest incidence rate is Portugal, with an incidence of 11 (per 100 000 inhabitants). It is one of the European countries with the highest incidence rate, alongside Slovakia and Poland. Spain ranks second with an incidence of 7.9 (per 100 000 inhabitants). Italy follows close behind with an incidence of 6.9 (per 100 000 inhabitants). Croatia, Greece and Cyprus have lower incidences, with rates of 6.8, 5.7 and 4.1(per 100 000 inhabitants) respectively.

Among Western European countries, France has the highest incidence rate at 10. (per 100 000 inhabitants). Belgium and the Netherlands are not far behind, with similarly high rates of 9.4 and 8.6, (per 100 000 inhabitants) respectively. Germany and Austria have much lower rates, with Germany at just 5.9 (per 100 000 inhabitants).

These data show that the highest incidence rates are in Eastern European countries. However, Portugal is the third country with the highest incidence in Europe, behind Slovakia and Hungary. France is just behind with a slightly lower incidence. (Figure 24)

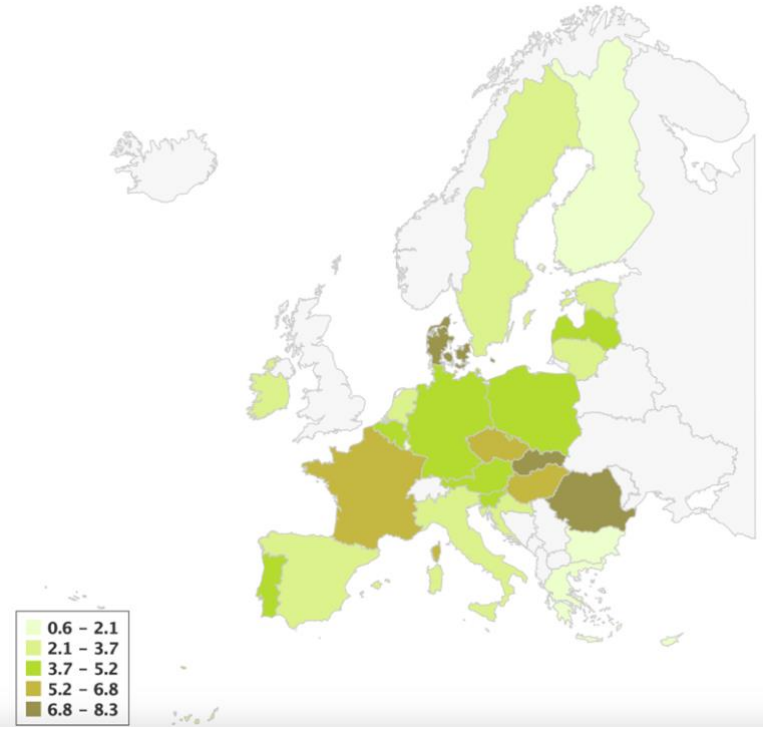


Figure 25.Estimated incidence of oropharyngeal cancer in Europe for both sexes and all ages in 2022 Data from the European Cancer Information System (ECIS). Rates are standardized on the European population (ESR, per 100 000 inhabitants). Source: European Commission, Joint Research Center (JRC). Available at: https://ecis.jrc.ec.europa.eu.

Oropharyngeal cancer is a cancer whose incidence has been increasing considerably for several years.

In Eastern Europe, Slovakia and Romania are the countries with the highest incidence rates, at 8.3 and 7.9 (per 100 000 inhabitants) respectively. Hungary and the Czech Republic have a lower incidence, but it is still quite high: 6.4 for Hungary and 5.3 for the Czech Republic (per 100 000 inhabitants).

With the exception of Denmark, where the incidence rate is 7.5 (per 100 000 inhabitants), the countries of Northern Europe have very low rates of oropharyngeal cancer. Rates range from 2 in Finland to 3.7 in Latvia (per 100 000 inhabitants).

Southern Europe is also relatively unaffected by this cancer. Spain and Italy have an incidence rate of 2.2, Cyprus 1 and Greece 0.6 (per 100 000 inhabitants). Portugal, although not having a very high incidence rate, remains the country most affected in this region, with a rate of 4.9 (per 100 000 inhabitants).

In Western Europe, France, with an incidence of 5.6, is ahead of Germany and Belgium, which have an incidence of 4.9 and 4.5 (per 100 000 inhabitants) respectively.

As with lip and OC, the countries most affected by oropharyngeal cancer are in Eastern Europe, with Slovakia in particular having the highest incidence of both.

France, on a European scale, remains a country with a fairly high incidence. Portugal, on the other hand, has a much lower incidence rate for this cancer, unlike lip and oral cavity cancer. (Figure 25)

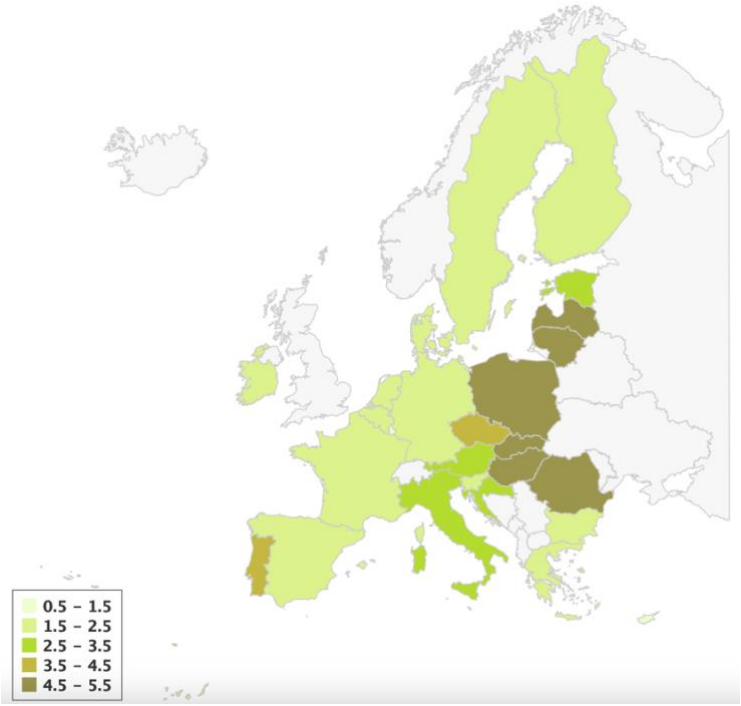


Figure 26. Estimated mortality of lip and oral cavity cancer in Europe for both sexes and all ages in 2022.
Data from the European Cancer Information System (ECIS). Rates are standardized on the European population (ESR, per 100 000 inhabitants). Source: European Commission, Joint Research Center (JRC). Available at: https://ecis.jrc.ec.europa.eu.

Eastern European countries have the highest mortality rates in Europe. Slovakia, Poland, Hungary and Romania have mortality rates ranging from 4.8 for Romania to 5.5 for Slovakia (per 100 000 inhabitants).

Among the northern countries, Lithuania and Latvia also have very high mortality rates, at 5.2 for Lithuania and 4.9 for Latvia. Estonia has a rate of 3.1, while Sweden and Finland have relatively low rates of 2.3 and 2 (per 100 000 inhabitants).

In the south, Portugal is the country with the highest mortality rate, at 3.5 (per 100 000 inhabitants). It is closely followed by Croatia, with a rate of 3.3 (per 100 000 inhabitants). With rates of around 2.5 (per 100 000 inhabitants), Italy and Spain are also among the Southern European countries with the highest mortality rates.

In the west, Austria has the highest mortality rate, at 2.6 (per 100 000 inhabitants). It is followed by Germany and France with a mortality rate of 2.4, then Belgium and the Netherlands with rates of 2.1 and 2.7 (per 100 000 inhabitants) respectively

So, such as the incidence, Eastern European countries are the most affected by lip and oral cavity cancer mortality, far outstripping Portugal and France (Figure 26)

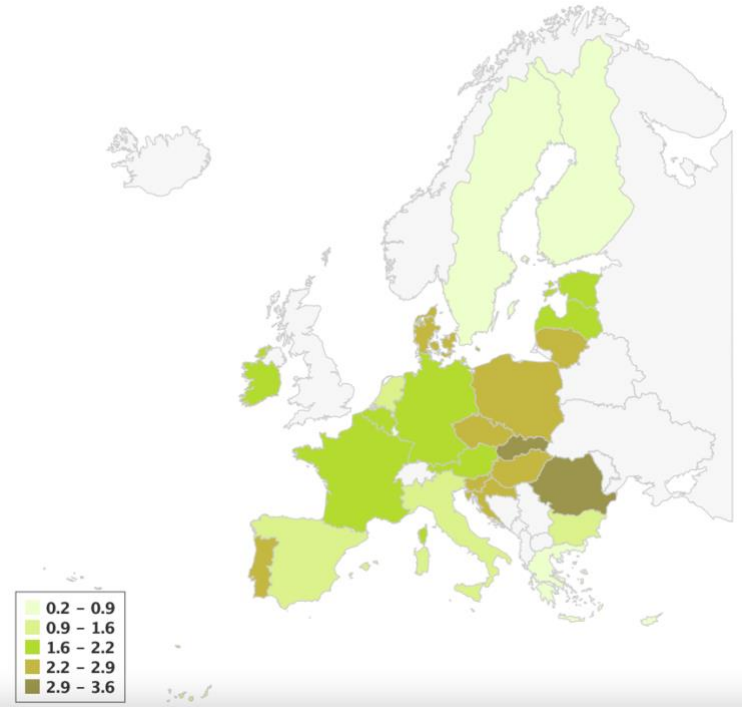


Figure 27. Estimated mortality of oropharyngeal cancer in Europe for both sexes and all ages in 2022 Data from the European Cancer Information System (ECIS). Rates are standardized on the European population (ESR, per 100 000 inhabitants). Source: European Commission, Joint Research Center (JRC). Available at: https://ecis.jrc.ec.europa.eu.

In Eastern Europe, mortality rates are very high, particularly in Romania and Slovakia, where they are 3.6 and 3.5 (per 100 000 inhabitants). Hungary, Poland and the Czech Republic also have relatively high mortality rates, at 2.8, 2.3 and 2.2 (per 100 000 inhabitants) respectively.

Lithuania and Denmark are the northern European countries most affected by mortality. The mortality rate in these countries is 2.4 for Lithuania and 2.2 for Denmark (per 100 000 inhabitants). Latvia and Estonia are slightly less affected by mortality (2.1 and 1.6) per 100 000 inhabitants. Sweden and Finland, like their incidence rates, have very low mortality rates of 0.7 and 0.6 (per 100 000 inhabitants), making them the northern countries least affected by mortality.

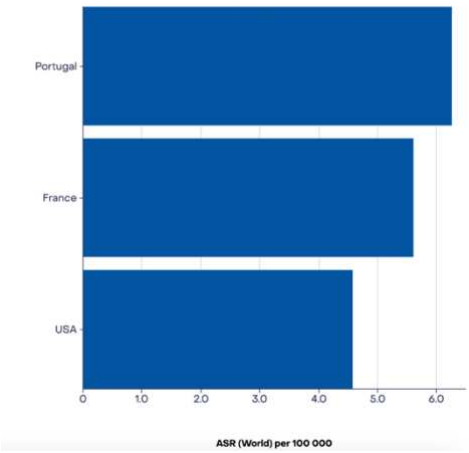
Southern Europe presents a contrast, with Slovenia, Croatia, and Portugal having incidence rates ranging from 2.3 to 2.6 (per 100 000 inhabitants), while Spain, Italy,

Greece, and Cyprus have relatively low rates; around 1.2 for Spain and Italy and less than 0.5 for the latter two (per 100 000 inhabitants).

In Western Europe, Austria and Germany are the most affected countries with a mortality rate of 2.1 (per 100 000 inhabitants). They are followed by France and Belgium with rates of 1.7 and 1.6 (per 100 000 inhabitants) respectively. The Netherlands has a lower mortality rate, at 1.2 (per 100 000 inhabitants).

Overall, as with incidence, Eastern European countries have a very high mortality rate, particularly compared with France. Portugal, for its part, has a fairly high mortality rate, but it is still lower than that of Eastern European countries. (Figure 27)

4.8.2. The United States



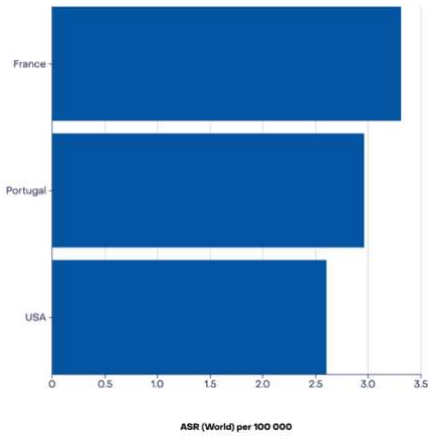
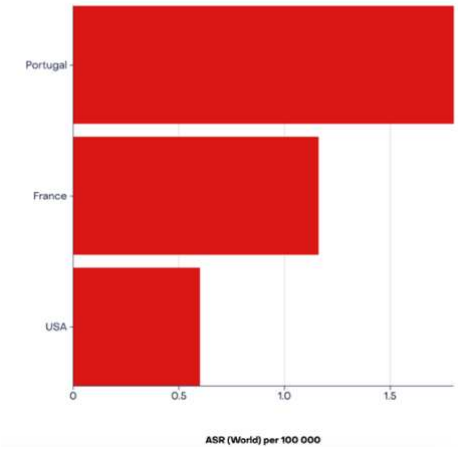


Figure 28a. Comparison of the incidence for lips and oral cavity cancer in Portugal and in France with the USA for both sexes and all ages in 2022
Figure 28b. Comparison of the incidence for oropharyngeal cancer in Portugal and in France with the USA for both sexes and all ages in 2022
Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer oobservatory. Available at: https://gco.iarc.fr/today

According to GBO data, the United States has a lower incidence rate of lip and oral cavity cancer than Portugal and France. Portugal has the highest incidence rate of the three countries, at 6.3 (per 100 000 inhabitants). France has a rate of 5.6 (per 100 000 inhabitants). The United States has a much lower rate of 4.6 (per 100 000 inhabitants).

For oropharyngeal cancer, the incidence rates are fairly similar, but France is the country with the highest incidence, at 3.3 (per 100 000 inhabitants). Portugal follows with an

incidence of 3, and the United States has an incidence of 2.6 (per 100 000 inhabitants) (Figure 28a/b).



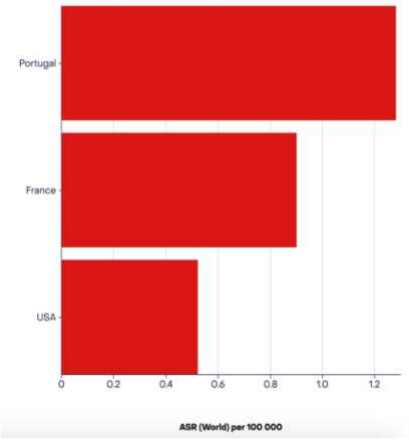


Figure 29a. Comparison of the mortality for lips and oral cavity cancer in Portugal and in France with the USA for both sexes and all ages in 2022
Figure 29b. Comparison of the mortality for oropharyngeal cancer in Portugal and in France with the USA for both sexes and all ages in 2022
Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatory. Available at: https://gco.iarc.fr/today

The same applies to mortality from cancer of the lips and oral cavity. The United States has a much lower mortality rate than Portugal and France. With a rate of 1.2, France has twice the mortality rate of the United States. Portugal, meanwhile, has an even higher rate of 1.8 (per 100 000 inhabitants).

For oropharyngeal cancer, Portugal has a mortality rate more than twice as high (1.3) as that of the United States (0.52) per 100 000 inhabitants. France is in the middle, with a mortality rate of 0.9 (per 100 000 inhabitants) (Figure 29a/b)

4.8.3. Asia

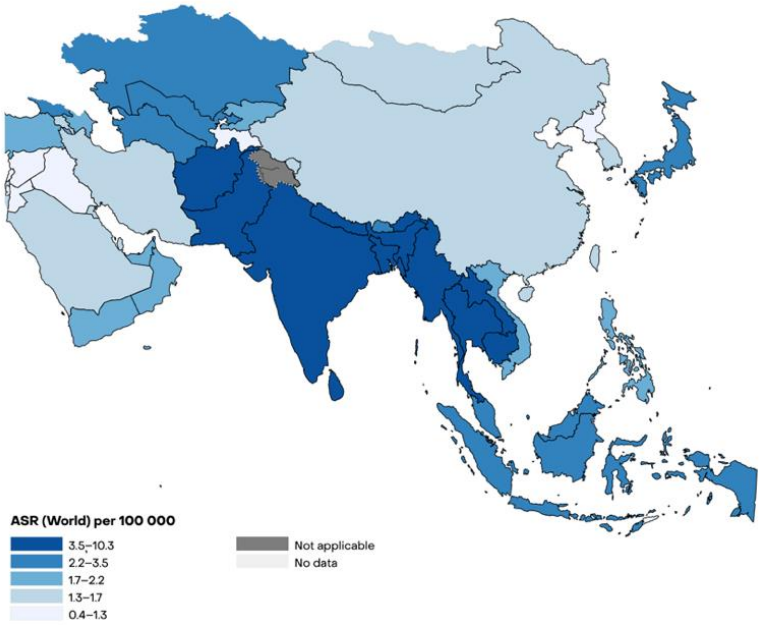


Figure 30. Estimated incidence for lips and oral cavity cancer in Asia for both sexes, all ages, in 2022 Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatory. Available at: https://gco.iarc.fr/today

Asia, divided into five regions, has the highest incidence of cancer in the world. South Asia is the region most affected. Bangladesh has the highest incidence of lip and OC in the world, at 10.3 (per 100 000 inhabitants). India, Pakistan and Sri Lanka also have extremely high rates, at 9.9, 9.2 and 8.1 (per 100 000 inhabitants) respectively.

In South-East Asia, the countries most affected are Myanmar with an incidence of 4.4, Cambodia with an incidence of 3.9 and Thailand with an incidence of 3.6 (per 100 000 inhabitants).

In the East, Japan has a fairly high incidence of 3.1 (per 100 000 inhabitants). China has an incidence rate of 1.5 (per 100 000 inhabitants), making it one of the lowest on the continent.

Central Asia countries have an incidence of approximately 3 (per 100 000 inhabitants).

West Asia is the region of Asia where countries have a relatively low overall incidence for the continent. Rates vary from 2.1 for Turkey, 1.8 for Oman and Yemen to 1.2 for Iraq (per 100 000 inhabitants).

Comparing these rates with those of Portugal (6.3) and France (5.6) per 100 000 inhabitants, it can be seen that some Asian countries, particularly those in South Asia, have a much higher incidence than European countries.

However, in comparison with other Asian regions, Portugal and France have a relatively high incidence, which may be more than twice the incidence observed in some countries. (Figure 30)

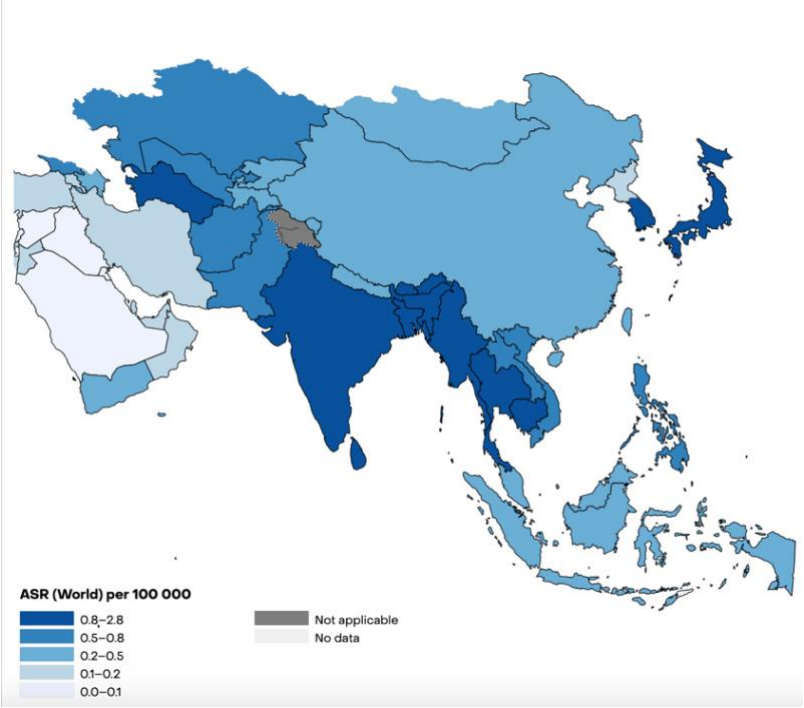


Figure 31. Estimated incidence for oropharyngeal cancer in Asia for both sexes, all ages, in 2022 Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatory. Available at: https://gco.iarc.fr/today

For oropharyngeal cancer, South Asia once again has the highest rates. Bangladesh, with a rate of 2.8, has the highest incidence on the continent. India and Sri Lanka follow with rates of 1.6 and 1.5 (per 100 000 inhabitants).

In Southeast Asia, Myanmar has an incidence of 1.2, Thailand 0.89 and Cambodia 0.79 (per 100 000 inhabitants).

In the East, Japan and South Korea are the most affected countries by this cancer with an incidence rate of 0.97 and 0.77. China has a lower incidence, at 0.33 (per 100 000 inhabitants).

Turkmenistan is the Central Asian country with the highest incidence rate, at 0.96 (per 100 000 inhabitants).

In West Asia, Yemen has the highest incidence at 0.25 (per 100 000 inhabitants). Saudi Arabia has the lowest incidence in the region, at just 0.07 (per 100 000 inhabitants).

With an incidence of 3.3 (per 100 000 inhabitants) in France and 3 (per 100 000 inhabitants) in Portugal, Asian countries are less affected by oropharyngeal cancer. (Figure 31)

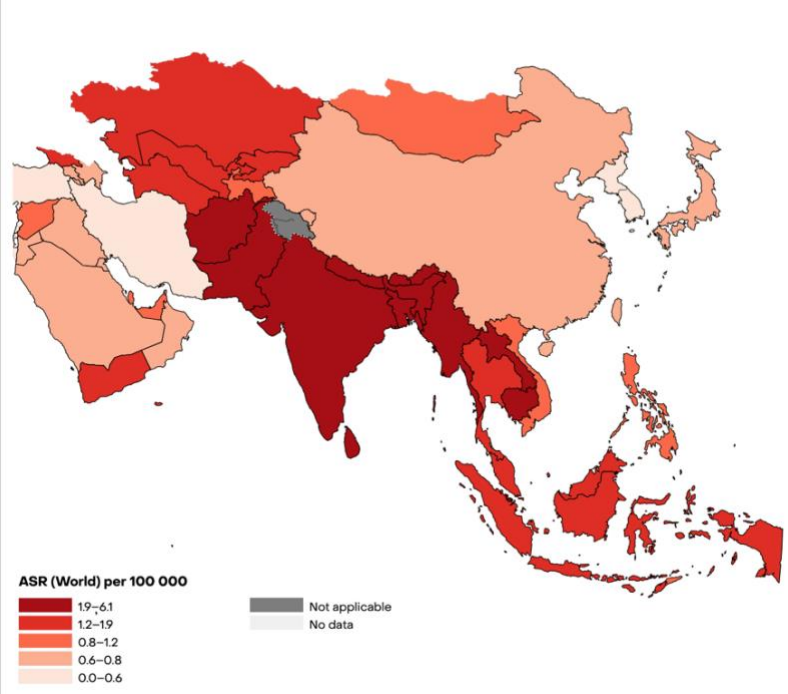


Figure 32. Estimated mortality for lips and oral cavity cancer in Asia for both sexes, all ages, in 2022 Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatory. Available at: https://gco.iarc.fr/today

Both mortality and incidence are highest in South Asian countries. Bangladesh, Pakistan and India are the most affected by mortality, with rates of 6.1, 5.9 and 5.6 (per 100 000 inhabitants) respectively.

In the Southeast, Myanmar and Cambodia are the hardest hit, with a mortality rate of 2.6 (per 100 000 inhabitants).

East Asian countries are very little affected by mortality, as rates do not exceed 0.78 (per 100 000 inhabitants).
Central Asian countries have an average mortality of 1.5 (per 100 000 inhabitants).
In the West, Yemen has the highest mortality rate at 1.3 (per 100 000 inhabitants).

With mortality rates of 1.8 (per 100 000 inhabitants) and 1.2 (per 100 000 inhabitants), Portugal and France have much lower mortality rates than South Asian countries, which are more than twice as high. Mortality in European countries is similar to that in West and Central Asia, but higher than in East Asia. (Figure 32)

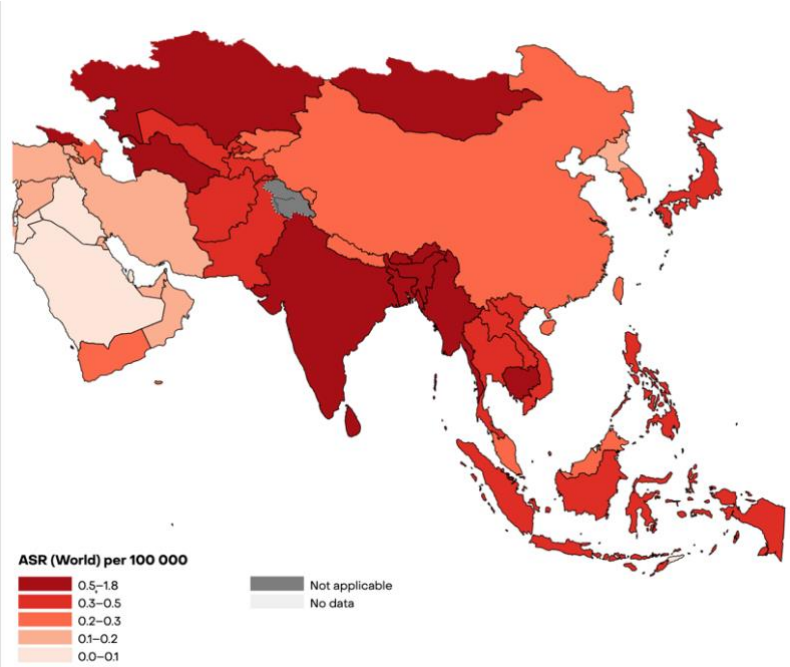


Figure 33. Estimated mortality for oropharyngeal cancer in Asia for both sexes, all ages, in 2022 Data extracted from GLOBOCAN (IARC). Rates are standardized according to world population (ASR, per 100 000 inhabitants). Source: International Agency for Research on cancer, Global Cancer Observatory. Available at: https://gco.iarc.fr/today

In the case of oropharyngeal cancer, mortality rates are still highest in the southern region, with Bangladesh, India and Sri Lanka recording rates of 1.8, 1 and 0.78 (per 100 000 inhabitants) respectively.
In the South-East, Cambodia is the most affected by mortality, with a rate of 0.50 (per 100 000 inhabitants).

Japan is the most affected East Asian country, with a mortality of 0.34; China has a mortality of 0.19 (per 100 000 inhabitants).
Central Asia is also quite affected by mortality, with Turkmenistan seeing its rate rise to 0.77 (per 100 000 inhabitants).
West Asia, on the other hand, has a very low mortality rate, particularly in Saudi Arabia and Iraq, with rates of 0.06 and 0.05 (per 100 000 inhabitants) respectively. Yemen is the most affected country in the region, with a rate of 0.21 (per 100 000 inhabitants).

With a mortality rate of 1.3 and 1.2 (per 100 000 inhabitants) respectively, Portugal and France have relatively high mortality rates compared with Asian countries. With the exception of Bangladesh, Asian countries all have much lower mortality than European countries. (Figure 33)

4.9. Descriptive analysis of survival by place of residence

Survival is a variable that can differ depending on the country and the type of cancer. For our work, the latest survival data from ECIS are between 2000 and 2007 for France and Portugal.

In the case of OC, there is a slight variation between the rates in Portugal and France. For men aged 15 to 44, the Portuguese survival rate is 44.46%; for French men of the same age, the rate is a bit lower at 41.1%. In the 45-54 age group, France has a slightly higher survival rate at 37.28%, compared with 31.76% for Portugal. Among the over-55s, Portugal has a better survival rate than France, particularly among the over-75s, where the Portuguese survival rate is 33.87%, compared with just 25% for the French population. In young women (aged 15-44), the survival rate is quite high, at 70.4% for French women and 61.46% for Portuguese women. In the 45-54 age group, the rates are similar, although Portugal has a slightly higher survival rate, 65.28% compared with 62.5% in France. The gap widens in the 65-74 age group, with a survival rate of 65.17% in Portugal and only 51.13% in France.
Women have a much higher survival rate than men in both countries.

For oropharyngeal cancer, French men have a much better survival rate than Portuguese men. In fact, among 15–44-year-olds, the French survival rate is 46.91%, but only 31.59% for the Portuguese. The biggest difference is in the 45-54 age group, with a survival rate of 43.63% in France versus less than 25% in Portugal. The trend is reversed for the over-75s, with a survival rate of 33.9% for the Portuguese and 27.32% for the French. For women aged between 15 and 44, the French survival rate is just over 50%, compared with 43.12% in Portugal. Among 45–54-year-olds, the Portuguese survival rate is 42.92%, but the French rate falls to 39.31%. It rises to 53.68% for 55–64-year-olds, a rate similar to Portugal's. Between the ages of 65 and 74, the survival rate for this cancer is 50.82% in Portugal, but only 42.55% in France. No data is available for Portuguese women over 75. For French women, survival is only 36.44%.
Even if women once again have a higher survival rate than men, there is some variability in oropharyngeal cancer rates between different age groups.

As we have no official data on survival rates in Asia and the USA for the period 2000-2007, we can provide, for information purposes, the 5-year survival rate in Asia between 2008 and 2012 and in the USA between 2012 and 2018.
In Asia, South Korea has the highest survival rate at 57.1%. Bahrain and Turkey follow at 51.1% and 50.4% respectively. A little further down the list, with a survival rate of 40.5%, we find China, followed by India at 36.1%. Thailand has a relatively low survival rate at 25%.
In the USA, cancer of the oral cavity has been divided into three parts: the lips (5-year survival rate: 91%), the tongue (5-year survival rate: 69%) and the floor of the mouth (5-year survival rate: 53%). For the oropharynx, the 5-year survival rate over the same period was 52%.

5. Discussion

From the data studied, Portugal has a higher incidence of lip and oral cavity cancer than France. In fact, the total incidence is 6.3 (per 100,000 inhabitants) in Portugal, compared with 5.6 (per 100,000 inhabitants) in France. Men are the most affected, with an incidence of 10.6 (per 100,000 inhabitants) in Portugal and 8.3 (per 100,000 inhabitants) in France. However, women are the most affected in France, with an incidence of 3.1 versus 2.4 (per 100,000 inhabitants) in Portugal.

In the 20-29 and 30-44 age groups, Portugal has a higher incidence than France. Men are still the most affected, particularly in the 30-44 age group, with an incidence of 10.7 (per 100,000 inhabitants) in Portugal, compared with 2.7 (per 100,000 inhabitants) in France. However, the trend is reversed in the 45-64 age group and in the over-65s. In the 45-64 age group, the Portuguese incidence is 17.2 (per 100,000 inhabitants), while the French incidence is 17.7 (per 100,000 inhabitants). Men are always the most affected in Portugal, but women are in the majority in France (9.1 per 100,000 inhabitants) compared with 5.4 (per 100,000 inhabitants) in Portugal.

The situation is the same for people over 65.

For oropharyngeal cancer, Portuguese men are in the majority, with a total incidence of 6 (per 100,000 inhabitants), while French men have an incidence of 5.2 (per 100,000 inhabitants). However, women are more affected in France (1.6 per 100,000 inhabitants) than in Portugal (0.35 per 100,000 inhabitants). Most people affected by this cancer are over 65.

Concerning the total number of cases of the lip and oral cavity cancer, France had a total of 6115 cases in 2022, compared with only 1055 cases in Portugal. In the 20-29 age group, data is almost identical in both countries, with 9 cases in France and 7 in Portugal.

Men are still the most affected, with 2025 cases among 45–64-year-olds in France, compared with just 369 in Portugal. The over-65s are the most affected by this cancer, with a total of 3,165 cases in France, including 1,854 men and 1,311 women. In Portugal, there are a total of 503 cases, including 303 men and 200 women in the same age group.

Oropharyngeal cancer also affects France much more than Portugal, with 3 342 cases recorded in 2022 in France versus 475 in Portugal.

No data is available for 20–29-year-olds in either country, but this cancer mainly affects the 45-64 age group, with men being the most affected: 1 899 cases in France, 3/4 of them men. In Portugal, 258 cases have been recorded, 244 of them in men and 14 in women. This significant difference between the two countries can be explained by the fact that Portugal has a population more than six times smaller than that of France

The Portuguese population is slightly more affected by lip and oral cavity cancer mortality than France.
In fact, with a total mortality rate of 1.8, including 3.1 and 0.63 (per 100,000 inhabitants), Portugal is slightly ahead of France, with mortality rates of 1.2, 3.1 and 0.63 (per 100,000 inhabitants) respectively.
The oldest population (+65) is the most affected by mortality, particularly men, with a mortality rate of 14.4 (per 100,000 inhabitants) for Portuguese men and 10.6 (per 100,000 inhabitants) for French men. For women, these rates are 5.1 and 4.3 (per 100,000 inhabitants) respectively.
An exception can be seen in the 45-64 age group, where French women have a very slightly higher mortality rate than Portuguese women, 1.4 to 1.3 (per 100,000 inhabitants).
Mortality from oropharyngeal cancer once again affects men in the majority, and the Portuguese population remains the most affected. However, in the 45-64 and over-65 age groups, French women have a much higher mortality rate than Portuguese women. In fact, in the 45-64 age group, the mortality rate is 1.3 (per 100,000 inhabitants) for French women, compared with just 0.36 (per 100,000 inhabitants) for Portuguese women. The same applies to the over-65s, where French women have a mortality rate of 2.1 (per 100,000 inhabitants), while Portuguese women have a low rate of 0.69 (per 100,000 inhabitants).

According to the table presenting data from 2010 and 2022, it is evident that the incidence has significantly decreased between these two years for both Portugal and France.

This decrease in incidence between 2010 and 2022 can potentially be explained by HPV vaccination campaigns. Mortality also declined significantly in both countries between 2010 and 2022.

Geographical and temporal disparities in lip, oral cavity and oropharyngeal cancers reflect the complex interplay of lifestyle habits, public health infrastructures and new risk factors such as HPV. To better understand these differences, the following comparative table highlights the main trends in risk factors and prevention strategies in Portugal, France, the USA, Asia and the rest of Europe. This overview provides essential context for the analysis of national public health responses and cancer control strategies worldwide.

Table 11.Geographic Comparison of Lip, Oral Cavity, and Oropharyngeal Cancers

Region	Main risk factors	HPV impact	Prevention	Main explanatory factors
Portugal	Tobacco, alcohol	Emerging (mainly oropharyngeal)	Moderate	Traditional habits, late diagnosis, older population affected
France	Tobacco, alcohol	Increasing	Improving vaccination and awareness	Effective tobacco/ alcohol control, better access to care, HPV vaccination
Rest of Europe	Tobacco, alcohol	Moderate to high	Strong in Northern/Western countries	Strong anti-smoking policies, HPV vaccination, effective screening and dental care
United-States	HPV, less tobacco and alcohol than in Europe	High	Strong	HPV epidemic in men, strong prevention system, early diagnosis, access to advanced treatment

Asia	Smokeless tobacco, POH	Low to moderate (less documented)	Low in rural areas	Cultural use of betel/ tobacco, limited access to prevention and early care

As the table shows, major disparities persist between different regions of the world. These differences are largely explained by regional variations in tobacco and alcohol consumption, access to healthcare and implementation of HPV vaccination programs. These vaccination programs are particularly prominent in Northern European countries, where incidence rates are much lower than in the rest of the continent. Understanding these trends is essential to developing appropriate public health strategies and reducing the global burden of these cancers.

These facts also enable us to understand the significant differences in incidence and mortality rates for cancers of the oral cavity and oropharynx observed between Portugal and France between 2010 and 2022. In Portugal, the higher rates are largely explained by historically high alcohol and tobacco consumption, combined with more advanced diagnoses and less widespread access to early detection services. Conversely, France has seen a decline in incidence and mortality, attributable to more aggressive public health campaigns, reduced tobacco and alcohol consumption and better access to care. However, France has seen an increase in HPV-related oropharyngeal cancers, particularly in men, who tend to have a better prognosis and are less associated with traditional behavioral risk factors. HPV vaccination programs and oral health education have been more widely implemented in France than in Portugal, contributing to better outcomes.

According to survival data, it appears that the survival rate in Portugal and France is higher in women for both cancers, and that despite some variations, it decreases with age.

Data from the Asian continent show that West Asia is the part of the continent with the highest survival rate, particularly in Turkey. Conversely, South Asia, particularly Thailand, is the region with the lowest survival rate.

6. Conclusion

This study clearly showed that cancers of the lip and oral cavity, as well as oropharyngeal cancer, are a real public health problem in Portugal, although epidemiological changes were observed between 2010 and 2022.
Analysis of data from GBO and ECIS reveals a stabilization with a slight decrease in incidence for certain age groups. However, a worrying increase in incidence is observed among younger people, particularly for oropharyngeal cancer linked to HPV exposure.

A comparison with data from France and other regions of the world (the United States, Asia, and the rest of Europe) highlights significant discrepancies in both incidence and mortality. These differences can be explained mainly by certain variability in risk factors (tobacco, alcohol, sexual behavior), prevention policies, and access to care.

Despite high mortality, particularly among men over 65, efforts in early detection, oral health education, and prevention of risky behaviors must be intensified to try to reverse the trend in the long term.
In conclusion, this work demonstrates the importance of a preventive and multidisciplinary approach to combating oral and oropharyngeal cancer, whether in Portugal or anywhere else in the world. Epidemiological data must continue to be updated regularly in order to guide public health strategies for better prevention and treatment of these diseases.

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