INCIDENCE TRENDS OF HEAD AND NECK CANCER IN THE PROVINCES OF GIRONA AND TARRAGONA (1994-2018)

A population-based study

FINAL DEGREE PROJECT

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CONTENTS

1. ABSTRACT

Background: Head and neck cancer (HNC) appears to be decreasing in incidence in developed countries, with potential changes in aetiology proposed. This study aims to provide a regional approach of HNC incidence trends overall and by subsites, which may afford knowledge for preventative measures and leveraging resources in order to reduce the burden of HNCs.

Objectives: To determine the trends in incidence of HNC, both overall and by anatomical subsites based on the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) topographic codes, while also discerning variations between sexes between 1994 and 2018 in the population of the provinces of Girona and Tarragona.

Design: A population-based retrospective observational cohort study conducted between December 2022 and January 2024.

Methods: 7966 cases of patients diagnosed with primary HNC from 1994 to 2018 were identified from the Cancer Registry of Girona (CRG) and Cancer Registry of Tarragona (CRT) database. Incidence has been estimated as Crude Rate (CR), Age-Standardized to the European population Incidence Rate ($ASIR_E$), Age-Standardized to the World population Incidence Rate ($ASIR_W$) and Age-specific rates (ASR). Incidence trends for overall HNC and by subsite were calculated subsequently through the Annual Percent Change (APC) of ASIR, expressed as a percentage increase or decrease with a 95% confidence interval (95% CI).

Results: A significant decrease in incidence, with an APC of -1.83, was observed between 1994 and 2018 in overall HNC. Incidence also exhibited a decline in lip, hypopharyngeal, laryngeal and salivary glands cancers. Among men, a significant decrease in incidence was observed between 1994 and 2018 in overall HNC, lip, oral cavity, nasopharyngeal, hypopharyngeal, laryngeal and salivary glands cancers. In women, a significant increase in incidence was identified for overall HNC, as well as for oral cavity, oropharyngeal, hypopharyngeal and laryngeal cancers, during the same period.

Conclusions: A significant decrease in the incidence of overall HNC, along with cancers affecting the lip, hypopharynx, larynx, and salivary glands, has been observed in the provinces of Girona and Tarragona from 1998 to 2018. During this period, the general trend observed among men is declining, whilst the general trend observed in women is rising.

Key words: epidemiology, head and neck cancer, trends, incidence, risk factors.

2. ABBREVIATIONS

ACC: Adenoid cystic carcinoma

APC: Annual Percent Change

$ASIR_E$: Age-Standardized to the European population Incidence Rate

$ASIR_W$: Age-Standardized to the World population Incidence Rate

ASR: Age-specific rates

CEIM: Comitè d'Ètica d'Investigació amb Medicaments de Girona

CI: Confidence interval

CR: Crude rate

CRG: Cancer registry of Girona

CRT: Cancer registry of Tarragona

DCN: Death-Certificate Notification

DCO: Death-Certificate-Only

GEDGPC: Grup d'Epidemiologia Descriptiva, Genètica i Prevenció del Càncer

E6: Early Oncoprotein 6

E7: Early Oncoprotein 7

EBV: Epstein-Barr virus

EGFR: Epidermal Growth Factor Receptor

ENCR: European Network of Cancer Registries

GCS: Golestan Cohort Study

HAA: Heterocyclic aromatic amines

HIV: Human immunodeficiency virus

HNC: Head and neck cancer

HNSCC: Head and neck squamous cell carcinoma

HV: Histological verification

IACR: International Association of Cancer Registries

IARC: International Agency of Research on Cancer

IDESCAT: Institut d'Estadística de Catalunya

ICD-O-3: International Classification of Diseases for Oncology, 3rd edition

IdIBGi: Institut d'Investigació Biomèdica de Girona

INHANCE: International Head and Neck Cancer Epidemiology consortium

IQR: Interquartile range

IR: Incidence rate

N: Number of cases

NEC: Neuroendocrine carcinoma

NOC: N-nitroso-compounds

NOS: Not Otherwise Specified

OPC: Oropharyngeal Cancer

SD: Standard Deviation

UK: United Kingdom

NPC: Nasopharyngeal cancers

OCC: Oral cavity cancer

OR: Odds ratio

p16: p16INK4a protein

PAHs: Polycyclic aromatic hydrocarbons

REDECAN: Red Española de Registros del Cáncer

SCC: Squamous cell carcinoma

SEER: Surveillance Epidemiology and End Results Program

SEPC: Servei d'Epidemiologia i Prevenció del Càncer de Tarragona

SNHS: Spanish National Health Survey

TCGA: The Cancer Genome Atlas program

UERCG: Unitat d'Epidemiologia I Registre de Càncer de Girona

US: United States

WHO: World Health Organisation

3. INTRODUCTION

3.1 GENERAL ASPECTS OF HEAD AND NECK CANCER

Head and neck cancer (HNC) is a group of epithelial malignancies that originate in the upper aerodigestive tract, including the oral cavity, pharynx, larynx, the paranasal sinuses and the salivary glands (1). HNC is the seventh most common type of cancer worldwide accounting for an estimated 890,000 new cases a year (2). The incidence of HNC varies widely by subsite, geographical location, and demographic characteristics (3).

In recent decades, several studies have shown that, in men, incidence trends for non-Human Papillomavirus (HPV) related HNCs declined in almost every country, while in women, incidence trends increased in both HPV-related and non-HPV-related cancers in different geographical areas, especially in Asian and European countries (4,5). However, there is limited information available on the trends in HNC incidence by subsite in specific regions of Spain.

3.1.1 Classification of head and neck cancer by anatomical subsite

HNC is a complex and heterogeneous group of malignancies that arises from various anatomic sites. To facilitate the study and treatment of HNC, it is important to have a standardized and internationally accepted system for classifying these tumours based on their topographical location and histopathology.

The International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) from the World Health Organisation (WHO), which may be consulted in *Annex 1,* is a comprehensive and widely used system that provides a standard framework for classifying and coding neoplasms (6). The system includes a four-digit code for the site of the primary tumor, with the first two digits representing the organ or tissue group and the second two digits representing the specific site within that group. It allows for the uniform recording of tumor characteristics, including the site of origin. The ICD-O-3 system is used by cancer registries worldwide and has been instrumental in facilitating the comparison of cancer incidence and mortality rates across different populations and regions.

According to the ICD-O-3 coding system, HNC is classified into several topographical sites based on their anatomic location. According to the TNM 8th Edition, the topographical sites of HNC are divided into several regions: the lip and oral cavity, the pharynx, the larynx, the nasal cavity and paranal sinuses, the major salivary glands, and the unknown primary (cervical nodes). The **lip** compasses the external upper and lower lip and the commissures. The **oral cavity** includes the tongue, floor of the mouth, gingiva, buccal mucosa, and hard palate. The **pharynx** is further divided into three subsites: the nasopharynx, the oropharynx, and the hypopharynx. The **nasopharynx** includes the posterosuperior pharyngeal wall (from the union of hard palates and soft to the base of the skull), the lateral pharyngeal wall (including the pharyngeal recess) and the upper surface of the soft palate. The **oropharynx** includes the base of the tongue, the vallecula, the tonsils, the inferior surface of the soft palate, the uvula, and the posterior pharyngeal wall. The **hypopharynx** includes the piriform sinus, the posterior pharyngeal wall, and the posterior cricoid region. The **larynx** is divided into three subsites: the supraglottis, the glottis, and the subglottis. The supraglottis includes the epiglottis, the false vocal cords, and the arytenoids. The glottis includes the true vocal cords and the anterior and posterior commissures. The subglottis includes the area inferior to the glottis and extends to the inferior border of the cricoid cartilage. The **paranasal sinuses** are the ethmoid sinus and maxillary sinus. The **major salivary glands** are the parotid gland, submandibular gland, and sublingual gland. Finally, the **unknown primary** is applied when there is histological confirmation of squamous cell carcinoma with lymph node metastases but without an identified primary carcinoma. Histological methods should be used to identify Epstein-Barr virus (EBV) and HPV/p16 related tumours. If there is evidence of EBV, the nasopharyngeal classification is applied. If there is evidence of HPV and positive immunohistochemistry p16 overexpression, the p16 positive oropharyngeal classification is applied (7).

Understanding the classification of HNC according to the ICD-O-3 coding system is important for several reasons. Not only allows for the accurate and consistent reporting of HNC incidence and mortality rates across different populations and regions, which means that it is crucial for identifying trends and patterns in the epidemiology of HNC and for evaluating the effectiveness of prevention and treatment strategies; but also can facilitate communication and collaboration among healthcare professionals and researchers who are involved in the management of HNC by using a common language and framework so they can better

understand and compare the characteristics and outcomes of different types of HNC. This system is essential for facilitating the study and treatment of HNC and for improving our understanding of the epidemiology, clinical presentation, and outcomes of these malignancies.

3.1.2 Head and neck cancer clinical presentation

Each of these sites mentioned before has unique anatomical and functional characteristics, which can influence the clinical presentation, diagnostic evaluation, and treatment options for HNC.

For example, laryngeal cancers commonly present with hoarseness or difficulty breathing, whereas pharyngeal cancers often present late with dysphagia or sore throat. Tumors of the oral cavity may cause pain, burning sensation, difficulty swallowing, tongue ulcers and changes in speech. Many often present with a painless neck node. Patients with HNC can present with non-specific symptoms or symptoms commonly associated with benign conditions, however, such as sore throat.

The anatomical sites affected are important for functions such as speech, swallowing, taste, and smell, so the cancers and their treatments may have considerable functional sequelae with subsequent impairment of quality life (1).

3.1.3 Histopathology of head and neck cancer

Histopathological features of HNC are closely linked to the clinical behaviour and prognosis of the disease. The most frequent histological type is squamous cell carcinoma (SCC), accounting for about 90% of HNC cases. It arises from the squamous cells that line the mucosal surfaces of the upper aerodigestive tract, such as the oral cavity, pharynx, and larynx (8). Other less common histological types of HNC are adenocarcinoma, mucoepidermoid carcinoma, and lymphoma. SCC are graded based on their degree of differentiation, which reflects the extent to which they resemble normal squamous cells. Well-differentiated SCC tumours resemble

normal cells closely and are associated with a better prognosis than poorly differentiated or undifferentiated tumours.

On the other side, adenocarcinomas are a group of tumours that arise from glandular cells and can occur in various sites of the head and neck, such as the salivary glands, nasopharynx, and sinonasal cavity. They are less common than SCC tumours but can have a worse prognosis. Mucoepidermoid carcinoma is a malignant tumor that commonly arises from the glandular cells of the salivary glands and can also occur in other sites of the head and neck, such as the paranasal sinuses and the nasopharynx. It is characterized by a mix of mucus-secreting and squamous cells and can have variable biological behaviour. Lymphomas are a group of malignant tumours that arise from lymphocytes, a type of immune cell. They can occur in various sites of the head and neck, such as the tonsils, nasopharynx, and salivary glands. They are also less common than SCC tumours but can have a favourable response to therapy.

Adenoid Cystic Carcinoma (ACC) is a rare subtype of HNC that arises from the salivary glands. ACC is characterized by slow growth and perineural invasion. Neuroendocrine Carcinoma (NEC) is another rare subtype of HNC that arises from the neuroendocrine cells that are present in various sites of the head and neck region, such as the larynx, nasopharynx, and paranasal sinuses.

The histological grade of HNC is determined by assessing the degree of differentiation and architectural organization of the tumor cells. Well-differentiated tumours resemble the normal tissue of origin and have a better prognosis than poorly differentiated or undifferentiated tumours, which have a higher likelihood of invasion and metastasis. In addition, certain histological features, such as perineural invasion, lymphovascular invasion, and tumor budding, are associated with an increased risk of recurrence and poor survival (9,10). For further information on the different morphologies of head and neck tumours, please refer to *Annexes 3-12.*

Understanding the histopathology of HNC is essential for accurate diagnosis, staging, and treatment planning, and can provide valuable prognostic information for patients with this disease.

3.1.4 Molecular and genetic features of head and neck cancer

HNC is a multistep process proceeding from single gene mutations generated by carcinogens to the substantial dysregulation of metabolic processes. HNC forms after accumulation of genetic events which are accelerated by genomic instability related to carcinogen exposures, particularly tobacco and alcohol. These tumors may occur throughout the upper aerodigestive tract (oral cavity, oropharynx, larynx) and are found in older patients, usually with smoking or alcohol use history. They are also associated with p53 mutations and poor clinical outcomes.

Recently, HPV has been associated with a subset of HNC chiefly in the oropharynx and primarily in younger, white, non-smokers. HPV is a double stranded DNA virus which infects the squamous epithelium. High-risk subtypes, particularly HPV-16 and HPV-18, are associated with development of malignancy, both HNC and cervical cancer. The mechanism of oncogenesis is attributed to viral proteins E6 (which binds and degrades p53) and E7 (which inhibits retinoblastoma protein, a tumor suppressor gene that inhibits cell cycle progression). Patients with HPV-related HNC have improved prognosis with longer overall survival, decreased rate of recurrence, and improved response to chemoradiation (11,12).

There are genetic and prognostic differences between HPV-positive and HPV-negative HNC (13). The heterogenicity of this cancer, suggests a critical role for genetic alterations contributing to its carcinogenesis. The Cancer Genome Atlas (TCGA) Research Network showed that HPV-positive tumours harboured fewer mutations compared to HPV-negative tumours. TP53 mutations are found almost exclusively in HPV-negative tumours while activating mutations and amplifications of PIK3CA are more common in HPV-positive tumours.

The most common genetic alterations associated with HNC include mutations in the TP53 tumour suppressor gene, which plays a critical role in regulating cell cycle progression and DNA repair, and alterations in the CDKN2A tumor suppressor pathway, associated with promoter methylation as a mechanism of downregulation. Other commonly altered genes in HNC include those involved in cell signalling pathways, such as EGFR, RAS, and PIK3CA.

Understanding the mutational, genomic and transcriptomic landscape of HNC has leveraged better therapeutic approaches to manage this group of diseases, and it is hoped that additional insight into the molecular subtypes of HNC and its specific subsites will further drive improved strategies to stratify and treat patients with this debilitating disease (13)

3.2 EPIDEMIOLOGY AND ETIOLOGY OF HEAD AND NECK CANCER

3.2.1 Geographic distribution of head and neck cancer by subsite in the general population and in subpopulations

Per the latest GLOBOCAN estimates (2020), HNC is the seventh most common cancer globally, accounting for an estimated 890,000 new cases (roughly 4.5% of all cancer diagnoses around the world) and 450,000 deaths per year (roughly 4.6% of global cancer deaths). The incidence includes approximately 380,000 cases of cancer of the lip and oral cavity, 185,000 of the larynx, 133,000 of the nasopharynx, 98,000 of the oropharynx, 84,000 of the hypopharynx, and 54,000 of the salivary glands (2).

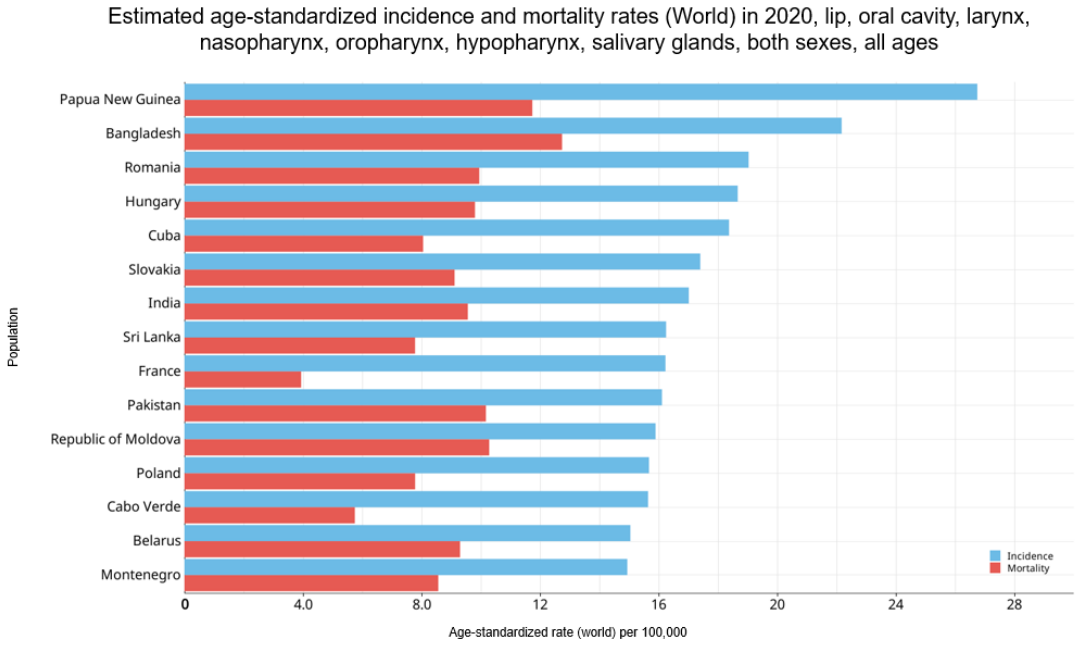


Figure 1. Bar chart showing estimated age-standardized incidence and mortality rates (world) in 2020 for lip, oral cavity, nasopharynx, oropharynx, hypopharynx, and salivary glands cancers, including both sexes and all ages. Data obtained from Globocan 2020 *(14)*.

The incidence and mortality rates of HNC vary widely by geographic region and demographic characteristics. Globally, HNC is more common in men than in women, with a male-to-female ratio of approximately 2:1, and in adults over 50 years of age (2). The incidence rates of HNC are highest in South and Southeast Asia (where the chewing of the carcinogenic areca nut is prevalent) (15), followed by Central and Eastern Europe, and South America (2).

Southeast Asia and Asia-Pacific regions have a particularly high incidence of oral cancer, associated with chewing of areca nut (betel quid), with or without tobacco (16). Oral cancer is therefore expected to rise within Southeast Asia, in line with population growth (15). The highest incidence rates are observed in India, where tobacco (with or without the areca nut) accounts for up to 80% of all HNC cases (17).

The global incidence of HNC has been increasing in many countries, particularly in younger populations, with a predicted 30% annual increase in incidence by 2030 (2). This increase has been recorded across developing countries (18). This trend is partly attributed to changes in lifestyle factors, such as increased alcohol consumption and tobacco use in developing nations, as well as the growing prevalence of HPV-related oropharyngeal cancer. It is estimated that HPV will overtake tobacco as the leading contributor to the global HNC cancer burden, causing the incidence of oropharyngeal cancer to surpass that of oral cancer (which is predominantly tobacco-related) (2,19). Similarly, over the past decade, laryngeal cancer cases have increased by 23%. Younger women in developed nations have seen a marked growth in incidence, likely due to changes in sex-specific cultural expectations for tobacco and alcohol consumption as well as a growing HPV burden (20,21). However, age-adjusted rates for new laryngeal cancer cases have been falling in countries with a higher sociodemographic index, again reflecting changes in smoking and alcohol drinking behaviour (19).

For men in developing countries, lip and oral cavity cancer is the second most common cancer (10 per 100,000). In Japan, the incidence of oropharyngeal, oral cavity, and salivary gland tumours has gone up, more for women than men, while nasopharyngeal and laryngeal tumor incidence has gone down (which are more associated with the EBV in East Asian populations than with HPV) (22). Likewise, in the United Kingdom (UK), oropharyngeal cancer (OPC) has increased by 7.3% among men and 6.5% among women, and oral cancer has increased by 2.8% and 3.0% for men and women, respectively, with the greatest growth seen in those of lower socioeconomic status (23,24).

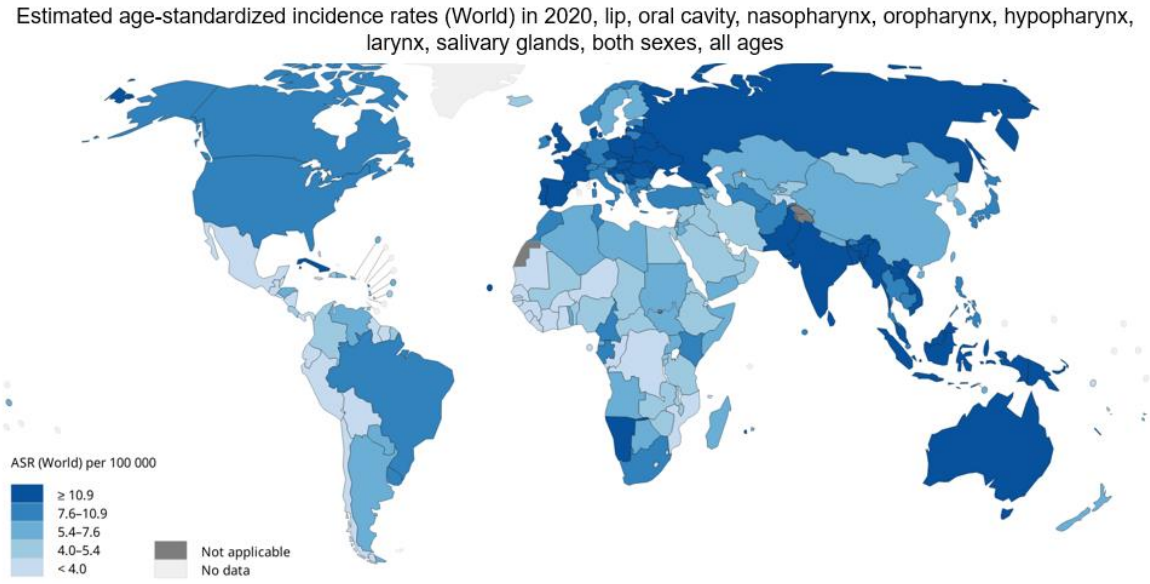


Figure 2. Map showing estimated age-standardized incidence rates (world) in 2020 for lip, oral cavity, nasopharynx, oropharynx, hypopharynx, and salivary gland cancers, including both sexes and all ages. Data obtained from Globocan 2020. *(14)*. ASR: Age-standardized rate

In the United States, since 1975 HNC mortality has fallen by 44%, down to a mortality rate of 2.5/100,000 persons in 2020. This has been accompanied by an increase in 5-year survival from 54.6% in 1975 to 68% in 2018. Survival rates remain disparate based on the stage of diagnosis. The 5-year survival for localized disease is 86.3%, decreasing to 69.0% for locally advanced and 40.4% for metastatic disease (25,26). The increase in survival among developed nations has been multifactorial, including the shift to HPV-related cases (which portend better prognosis), earlier detection due to screening, advances in robotic surgical resection and stereotactic radiation, as well as the development of immunotherapies (checkpoint inhibitors) for neoadjuvant (27), adjuvant (28), and metastatic systemic therapy (29,30). Access to screening and advanced therapies remains a contributor to disparate survival statistics, with racial minorities and those living in low-socioeconomic-status urban and rural communities (e.g., Appalachia) suffering greater incidence and lower overall survival (31,32). An analysis of HNC diagnoses at one academic institution during the COVID-19 pandemic suggested a larger proportion of late-stage diagnoses and worsened tumor burden following quarantine, potentially exacerbating disparities in survival (33).

3.2.2 Risk factors of head and neck cancer

The primary risk factors commonly linked to head and neck cancer encompass tobacco, alcohol consumption, using areca nut, HPV infection (particularly for OPC), and EBV infection (especially prevalent in Asia, particularly for nasopharyngeal cancers (NPC)).

Risk factors are generally similar across subsites of the head and neck, although the magnitude of risk associated with particular risks may vary, for example tobacco smoking risks are greatest for laryngeal cancer and alcohol for oral cavity and oropharyngeal cancer.

Tobacco

Tobacco use remains the leading risk factor for head and neck cancer, accounting for an estimated 75% of all cases according to a study of cases in Western Europe (34). However, this was slightly less for oral cavity cancer (64%) and slightly more for laryngeal cancer (89%) and much lower for women and among younger age groups (35). A national survey from the UK implicated tobacco in 70% of oral and pharyngeal HNC cases (36), while data from East Asia have implicated tobacco in 2.8–25% of cases. Tobacco use is increasing across developing nations as economic progress increases household disposable income. In developed nations, tobacco use has declined overall but increased in certain demographics, commonly women (37,38).

Tobacco contains numerous carcinogenic chemicals such as polycyclic aromatic hydrocarbons, nitrosamines, aromatic amines, and aldehydes which are released during high-temperature combustion that are known to damage DNA in the cells of the oropharynx and lead to the development of cancer. Heavy cigarette smokers have a 5–25-fold increased risk of HNC as compared to non-smokers (39), while pipe and cigar smokers are at a lesser, yet still increased, risk (40). Regular chewing tobacco use is also associated with a 1.7 odds ratio (OR) for HNC and 3.0 OR for oral cancer specifically (41). Reverse smoking, a habit practiced in certain areas of India and South America, in which the lighted end of the cigarette is kept inside the mouth while smoking, causes HNC involving the hard palate (42). Individuals with certain genetic and metabolic predispositions, including concurrent heavy drinking, are at the highest risk of developing HNC with smoking (40). Second-hand smoke exposure in childhood was found to

have a 1.28 OR for HNC, adjusted for smoking, drinking, and HPV status (43). Previous reports from the International Head and Neck Cancer Epidemiology Consortium (INHANCE) studies showed that active smoking is a stronger risk factor for laryngeal cancers than for oral cavity cancer among never alcohol drinkers (44).

Alcohol

Alcohol consumption among nonsmokers is estimated to account for 4% of head and cancer cases globally (45). The risk of HNC increases in a dose-dependent manner with the amount and frequency of alcohol consumption (relative risk 1.3× for all drinkers and 2.5× for heavy (>50 g/day) drinkers), with the highest risk observed among individuals who consume more than three alcoholic drinks per day (45). The risk of HNC also varies by the type of alcohol consumed, with higher risks observed among individuals who consume spirits (e.g., whiskey or vodka) than among those who consume beer or wine, although this effect may be nonsignificant when adjusted for alcohol concentration (44,46,47).

Alcohol's property as a solvent increases the mucosal tissue's susceptibility to carcinogens such as smoke or nitrites in food. Acetaldehyde, produced from ethanol by alcohol dehydrogenase, has also been shown to be mutagenic. Acetaldehyde is responsible for many of the symptoms of heavy alcohol consumption, such as headaches and flushing, and its conversion is blocked by disulfiram and other drugs with similar properties, such as metronidazole or abacavir, resulting in reactions with drinking (47,48). Interestingly, patients with variants in acetaldehyde dehydrogenase, the enzyme that breaks down acetaldehyde, have been found to be associated with greater HNC risk with heavy alcohol consumption, greater risk of resistance to chemoradiotherapy, and overall poor prognosis. Variants in acetaldehyde dehydrogenase are also responsible for the phenomenon of flushing with alcohol consumption, common in East Asian populations (48).

Recent analyses show that, consistently between sexes, drinking intensity was the predominant measure of alcohol affecting the risk of oral cavity, hypopharyngeal and laryngeal cancers, whereas the contribution of duration, for fixed alcohol intensities, was modest. Notably, this suggests that drinking alcohol beverages, even for a short period,

increases the risk at these cancer subsites and that duration of alcohol use has little or no consistent effect on the risk of these cancers (49).

Alcohol and tobacco have a multiplicative effect on head and neck squamous cell carcinoma (HNCSCC) when combined. Increases in alcohol and tobacco consumption are projected to be the major contributors to growing global HNC incidence over the coming decades, particularly in developing nations. Studies from the UK (36), China (37), and Lebanon (50) all implicate alcohol consumption in 32–37% of oropharyngeal HNC diagnoses, with approximately 90% of these cases also reporting a smoking history (45,51). Worldwide, tobacco or alcohol account for 72% (95% confidence interval (CI) 61–79%) of HNSCC cases, with 35% (nearly half) attributed to both combined (45). In fact, concurrent heavy alcohol and tobacco use has been shown to increase HNC risk 40-fold (47). Interestingly, among Black Americans, the association between cigarette smoking and HNC was greater than for White Americans, but the alcohol consumption risk was unchanged between the groups, suggesting differences in tobacco product quality or metabolism by race (52).

Areca Nut (Betel Quid)

In South and Southeast Asia and Polynesia, chewing of the areca nut, also known as betel quid, accounts for over half of oral and oropharyngeal head and neck cancer cases (53). The prevalence of consumption ranges from 33.8% in Sri Lanka to 76.8% in the Solomon Islands (54). Chewing can be part of rituals or recreational, as the compound has psychoactive effects via antagonism of GABA receptors, resulting in alertness, euphoria, and appetite suppression (55). In fact, around 600 million people chew areca nuts worldwide, and it is considered the fifth most commonly used psychoactive agent after alcohol, nicotine, caffeine, and cannabis. In some of these nations, Areca nut is the most affordable and accessible stimulant and appetite suppressant, thus making its usage particularly prevalent in rural and underprivileged populations (53,55). Areca nut can often be prepared with tobacco added, which may account for disparate risk calculations. A study from India found a 3× increased risk of HNSCC with areca chewing without tobacco and an 8× risk with tobacco, while a study from Taiwan reported a 10× risk without tobacco. Both studies reported positive dose–response curves (53).

Human Papillomavirus infection

HPV accounts for 72% of all head and neck cancer cases in developed nations, as compared to 13% of cases in developing nations (as indicated by p16 positivity on immunohistochemistry) (56). Over 20 high-risk HYPV serotypes have been identified, distinguished by the protein capsid. HPV16 is responsible for 85–90% of HPV related oropharyngeal HNC cases in North America, in contrast to cervical cancer where HPV16 and 18 both account for 50–75% of cases (57). The strongest association is found between HPV16 and palate cancer (58).

Oncogenesis occurs with viral infection of basal keratinocytes, exposed to micro-abrasions caused by sexual contact (59). The risk factors for HPV-associated oropharyngeal cancer include a history of multiple sexual partners, anal sex, oral sex (with the mouth on female genitalia conferring the highest risk), and a weakened immune system. Comorbidity with human immunodeficiency virus (HIV) is common, with women with HIV having a 1.5–2.5 times greater risk of HPV. Globally, those with >4 oral sex partners have an OR of 2.25 (95% CI 1.42–3.58) of HNC (60). The prevalence of HPV infection in oral cavity cancers is significantly smaller than OPC (61). The prevalence of HPV-associated oropharyngeal cancer has increased in developed nations in recent years (225% in the United States (US) from 1984 to 2004), particularly among young adults (62). In the US, HNC has surpassed cervical cancer as the leading HPV-associated cancer (63). Among US demographics, White men <45 years saw the greatest growth in incidence, with a 5.1% annual increase from 2008 to 2012. By contrast, the incidence of non-HPV associated HNC is roughly 50% higher among Black Americans (64). Likewise, in the UK, cases of HPV-related HNC rose by 51% from 1989 to 2006 (65).

HPV-positive HNCs are associated with greater infiltration of B-cells into the tumor microenvironment, have fewer genetic mutations, and have an intact apoptotic response, which may explain the improved prognosis and superior response to radio- and immunotherapy (59,66). HPV positivity portends a significantly longer median survival among HNC patients (130 vs. 20 months) (67), independently reducing the risk of death by 64% when adjusted for risk factors (68). HPV-positive HNC is now staged differently due to the large disparity in survival (69).

Ebstein Barr virus infection

Nasopharyngeal carcinoma, while uncommon in most populations, is prevalent in southern China, ranking among the most frequently diagnosed cancers in the region. Research has established the significant involvement of the EBV as the primary causative factor in the development of nasopharyngeal carcinoma.(3) Hence, the heightened prevalence of Epstein-Barr Virus (EBV) in Southeast Asia, specifically in China, correlates with an increased incidence of nasopharyngeal cancer, establishing the virus as one of the primary risk factors for this malignancy in these regions.

Immunodeficiency

Immunodeficiency resulting from HIV infection or solid organ transplantation has been linked to a heightened susceptibility to cancer in the head and neck area. HIV infected individuals exhibit a higher occurrence of various non-AIDS-defining malignancies. Notably, there is a two- to threefold rise in the incidence of HNC among HIV-infected patients. Similarly, individuals who have undergone solid organ transplantation face an elevated risk of developing cancer, including malignancies originating in the head and neck. Moreover, patients who have received a bone marrow transplant, despite lacking conventional risk factors, are at an increased risk of head and neck cancer, particularly in the oral cavity (70).

Opium

The use of opium has been linked to an elevated risk of laryngeal cancer. Opium, an illicit substance derived from the poppy plant, is obtained from the juice of the unripe seedpod and contains several alkaloids. According to the International Agency for Research on Cancer, opium is classified as carcinogenic to humans when smoked or consumed in various forms, including raw, dross, or sap opium. For instance, findings from the Golestan Cohort Study (GCS), which examined 50.045 patients in Iran, demonstrated that opium use was associated with an increased risk of developing laryngeal cancer that correlated with the dosage (71).

Racial differences

It has been well documented that in the US there are racial disparities in both HNC incidence and mortality (72). The most pronounced racial difference in HNC incidence is found in laryngeal cancer. Data from the Surveillance Epidemiology and End Results (SEER) Program show the age-adjusted incidence rates were highest among black men and women. The reasons for these differences in risk by race are not known, but could be due to differences in alcohol and alcohol metabolism, differing usage and cessation patterns by race (73).

Occupational socioeconomic disparities

The association between socioeconomic disadvantage (low education and/or income) and HNC is well established. Several studies have found consistently elevated risk associations for HNC with low occupational social prestige, low occupational socioeconomic position and manual work. These findings were only partly explained by smoking, alcohol drinking or working in recognised higher risk occupations. Moreover, health inequalities and cancer risks associated with socioeconomic factors have generally been observed to be stronger among men than women (74,75). Working in the craft and chemical industry, with direct exposure to wood dust and formaldehyde, may constitute a risk factor for head and neck cancer due to the carcinogenic nature of the chemicals involved. The risk associated with lower educational attainment is stronger for hypopharyngeal and laryngeal cancers than for oral cavity and oropharyngeal cancers and adjustment by smoking and alcohol attenuates substantially less for oropharyngeal cancer (76). This is consistent with the evidence related to the risk associated with smoking which shows a similar pattern.

Oral hygiene

Oral hygiene indicators, such as missing teeth, denture use, bleeding gums, infrequent dental visits, and tooth brushing infrequency, have been suspected to contribute to the aetiology of HNCs (77). Among the specific HNCs, the associations with oral hygiene were greatest for oral cavity cancers. The mechanisms by which poor oral hygiene is associated with HNC fall into categories of trauma and inflammation. Causes of trauma and inflammation are due to

coexisting disease and/or negligence of oral hygiene. Thus, these indicators may be indicative of dysbiotic shifts in the commensal oral microbiome, tooth wear, mechanical trauma, and general health maintenance, all of which are linked to cancer(78,79). In conclusion, good oral hygiene is associated with lower risk of HNC. Improvements in oral hygiene by increasing oral hygiene literacy, particularly for annual dentist visits and daily tooth brushing, may be protective against HNC, although the extent of risk reduction is modest (80).

Diet and nutrition

A wide number of studies have provided robust data suggesting an inverse association between the consumption of vegetables and fruits and the risk of HNC. In particular, patients reporting a diet without vegetables and fruits had double the probability of developing HNC when compared with subjects reporting daily intake of them (81). Similarly, lower cancer risks seem to be correlated with higher vegetable and/or fruit intake (82). Fruits and vegetables are composed of several bioactive compounds categorized into phytochemicals (e.g., phenolics, flavonoids, carotenoids), micronutrients (vitamins and minerals), and fibre (83). Most of these components can influence different stages of cancer onset and progression.

Although meat is an important source of protein, micronutrients (e.g., vitamin B6, vitamin B12), and minerals (e.g., zinc, iron, selenium, phosphorus), the process of cooking at high temperatures gives rise to the formation of carcinogenic substances, such as polycyclic aromatic hydrocarbons (PAHs), N-nitroso-compounds (NOC), and heterocyclic aromatic amines (HAA) (83).

Still, data regarding the relationship between the high consumption of red meat and processed meat and the risk of HNC are limited to a few studies with controversial results. A prospective study with a follow-up of over 20 years, however, reported a direct association between high intake of processed meat and HNC (84). Subjects reporting intake of processed meat three or more times a week were found to have a significantly increased risk of HNC compared with those without processed foods in their diets.

Genetic predisposition

The INHANCE carried out pooled analyses of epidemiological studies that confirmed the role of genetic predisposition in developing HNC. Although HNC arises sporadically, familial inheritance has been noted (85). A family history of HNC in a first degree relative is associated with a significant increased risk of developing the disease. Genetic polymorphisms in genes encoding enzymes involved in the metabolism of tobacco and alcohol have been linked with an increased risk of HNC. Furthermore, the risk of HNC increases in individuals with cancer susceptibility syndromes, such as hereditary non-polyposis colorectal cancer, Li-Fraumeni syndrome, Fanconi's anaemia, and ataxia telangiectasia (86).

Radiation

The administration of prior radiation therapy, weather for malignant or benign conditions, has been associated with an increased incidence of salivary glands cancer, SCCs and sarcomas. While this connection is indeed present, it should be noted that there is a considerable time delay before any potential adverse effects manifest, and the overall risk remains relatively low (3).

Other risk factors

Other interesting data to comment on would be the generally lower incidence and better prognosis of HNC in females than males, which may imply the protective role of estrogen, and the exogenous estrogen which may lower the risk of developing HNC (87,88). Also, the different incidence patterns between patients younger than 44 years and patients older than 44 years, which implied increased accumulative risk factor exposure and thus more genetic mutation accumulated and increased DNA methylation at age-related sites in the older generation (89). And also the increased incidence of advanced-stage cases, which may imply the more sensitive imaging detection adopted, instead of a more dismal clinical scenario (90).

Taking all this into account, it is of great interest and importance to report the dynamic incidence trend of HNC, which may reflect the impact of changing aetiology and the impact of different risk factors on HNC.

3.3 PREVENTION PLANS FOR HEAD AND NECK CANCER

As commented before, HNC represents the 7th most commonly diagnosed tumor type, and its incidence and mortality rates are on the rise in developing countries. This alarming trend can largely be attributed to preventable risk factors such as the ingestion of tobacco, alcohol, areca nut, and sexually-transmitted HPV infections (3). Thus, HNC prevention should aim to improve two fundamental domains of patient care: risk behaviour reduction to decrease HNC incidence (primary prevention) and accuracy and precision of early diagnostic detection (secondary prevention) (91).

3.3.1 Primary prevention

To address the escalating burden of HNC, it is imperative to implement comprehensive public health interventions. These interventions should predominantly focus on educating individuals about the risk associated with consuming carcinogenic agents, as well as promoting and facilitating smoking and areca nut cessation, decreasing alcohol consumption, implementing HPV vaccination and safe sex practices which are crucial in preventing HPV-related HNC, and maintaining good oral health and good nutritional habits.

According to INHANCE estimations, quitting tobacco smoking for one to four years reduces the risk of developing HNC, with further risk reduction at 20 years or more, at which time risk is similar to that of never smokers (1). Studies from Taiwan, India and China suggest that ceasing areca nut consumption would prevent roughly half of oral cancers in those nations.

Developed countries have been facing a rapid increase in the incidence of HPV-related HNC. Prophylactic use of 9vHPV is the most effective approach for preventing HPV-related HNC, since vaccination has been shown to reduce the prevalence of oral HPV 6, 11, 16 and 18 (the latter two being high-risk serotypes) by 88.2% (92).

Furthermore, numerous populations-based cohort studies from around the world have shown that consumption of a diversity of vegetables and fruits can decrease the risk of developing cancers of the larynx, oral cavity, and pharynx by up to 60%. What comes to say that interventions to improve the diet of the population should be one of the most important tools to prevent cancer (93).

3.3.2 Secondary prevention

Secondary HNC prevention should focus on two primary aims: identifying high-risk individuals and screening modalities.

The higher risk of developing HNC is having medical history of a primary HNC tumor, even after a lifestyle modification, previous HNC patients have a 2-7% increased risk of HNC second primary tumor per year. Reasons include shared risk factors such as tobacco and alcohol drinking, genetic instability and mutations, pre-existing genetic susceptibility, and immunodeficiency following chemotherapy, radiotherapy, immunosuppression for autoimmune diseases and transplant, and/or surgical treatments. Thus, the most effective and strategic approach aimed at HNC reduction here is to identify high-risk people and to inquire about risk factors (91).

So, it is important identifying and screening high-risk patients, since it can substantially contribute to early detection and timely intervention, also helping in reducing the HNC poor prognosis related to advanced-stages detection (3).

Taking all these factors into consideration, could be argued that in isolation, prevention might be equal, if not superior, to traditional treatment when calculating the total number of lives saved. Undoubtedly, it would additionally be superior when considering cost and morbidity (94).

4. JUSTIFICATION

Head and neck cancer encompasses a diverse group of malignancies originating from various anatomical sites, each potentially influenced by distinct risk factors. By analysing trends in incidence, we gain insights into the specific dynamics of these cancers, allowing for a more nuanced understanding of their epidemiology in the regions under study.

By focusing on subtypes related to anatomical sublocations, this study goes beyond a broad analysis of HNC as a collective entity. It explores whether certain subtypes are increasing or decreasing in incidence over the studied period, offering valuable information for public health planning. For instance, if oropharyngeal cancers show a rising trend, it prompts further investigation into the potential role of risk factors such as HPV infection.

The significance of this study extends beyond its immediate implications for preventive strategies. The detailed dataset generated can also serve as a foundational resource for future research. Researchers can leverage this information to explore the effectiveness of interventions, assess the impact of changing risk factor profiles, and contribute to the broader understanding of cancer epidemiology.

Furthermore, the population-based design of this study utilizes the database of the standardized cancer registry in the provinces of Girona and Tarragona, ensuring a robust and comprehensive dataset.

In conclusion, investigating the trends in head and neck cancer incidence in the populations of Girona and Tarragona over the past decades is not only a crucial step toward effective preventive strategies but also contributes to the understanding of the changing patterns of HNC in Girona and Tarragona as well as provides a foundation for future research in this field. By understanding the intricacies of regional variations, we pave the way for targeted interventions that can ultimately reduce the burden of head and neck cancer in these communities.

5. HYPOTHESES

5.1 MAIN HYPOTHESES

- The overall incidence of head and neck cancer has decreased in the provinces of Girona and Tarragona between 1994 and 2018.
- The incidence of lip, oral cavity, hypopharyngeal, laryngeal, NOS pharyngeal and sinonasal cancer has decreased in the populations of Girona and Tarragona provinces between 1994 and 2018.
- The incidence of salivary glands cancer has remained stable in the populations of Girona and Tarragona between 1994 and 2018.
- The incidence of oropharyngeal and nasopharyngeal cancer has increased in the populations of Girona and Tarragona between 1994 and 2018.
- The trends in incidence of overall HNC and by subsite are different between sexes.

5.2 SECONDARY HYPOTHESIS

- The incidence of overall head and neck cancer and by subsite have a different distribution in terms of age and sex in the populations of Girona and Tarragona between 1994 and 2018.

6. OBJECTIVES

6.1 MAIN OBJECTIVE

To determine the trends in incidence of overall head and neck cancer and by anatomical subsites according to the ICD-O-3 topographic codes, while discerning by sexes between 1994 and 2018 in the population of the provinces of Girona and Tarragona.

6.2 SECONDARY OBJECTIVE

To define the epidemiological characteristics of patients with overall head and neck cancer and by subsite in relation to age and sex distribution between 1994 and 2018 in the population of the provinces of Girona and Tarragona.

7. METHODS

7.1 STUDY DESIGN

A population-based analytical, observational and retrospective cohort study from December 2022 to January 2024 conducted by the "*Grup d'Epidemiologia Descriptiva, Genètica I Prevenció del Càncer (GEDGPC) de l'Institut d'Investigació Biomèdica de Girona*" (IdIBGi), which used data recorded in the Girona and Tarragona Cancer Registries, conducted in the provinces of Girona and Tarragona between 1994 and 2018.

7.2 STUDY SETTING

This study has been set in the cancer registries of the provinces of Girona and Tarragona. The Epidemiology and Cancer Registry Unit of Girona (UERCG), together with the Epidemiology and Cancer Prevention Service (SEPC) of Tarragona, collects and epidemiologically analyses information on the distribution of cancer in the regions of Girona and Tarragona, since the year 1994 and 1980, respectively.

7.3 STUDY POPULATION

The population of this study are patients diagnosed with head and neck cancer at any hospital in the province of Girona and Tarragona and recorded in the population-based Girona Cancer Registry and Tarragona Cancer Registry between January 1st, 1994 and December 31st, 2018.

7.4 CASE SELECTION

For the selection of the study cases, we retrieved data from the Cancer Registry of Girona (CRG) and the Cancer registry of Tarragona (CRT), which served as our database. Some of the inclusion and exclusion criteria of the study align with the inclusion and exclusion criteria used in the cancer registries of Girona and Tarragona:

Inclusion criteria

- Patients diagnosed with epithelial cancer of the head and neck in the provinces of Girona or Tarragona between 1994 and 2018, encoded by ICD-O-3 as: C00-C14; C30-C32 for topography.

Exclusion criteria

- Non-resident patients diagnosed in the provinces of Girona or Tarragona.
- Patients diagnosed with non-invasive head and neck cancer or non-clearly malignant (ICD-O-3 morphological behaviour code 0, 1 or 2).
- Patients diagnosed with head and neck cancer with histological confirmation of lymphoma or sarcoma (ICDO-O-3 morphology code 8800-9992).

To categorize the different topographies of head and neck cancer, we adhered to the classification of ICD-O-3 and grouped them as defined in *Table 1*.

Table 1. Codification for HNC according to the ICD-O-3 (6). ICD-O-3 coding is further explained in *Annex 1.*

Topographical site	ICD-O-3 code
Lip	C00.0-C00.6, C00.8-C00.9
Oral cavity	C02.0-C02.3, C02.8-C02.9. Tongue (excluding base and lingual tonsil) C03.0-C03.1, C03.9. Gum C04.0-C04.1, C04.8-C04.9. Floor of mouth C05.0, C05.8. Hard palate C06.0-C06.2, C06.8-C06.9. Other parts of the mouth
Salivary glands	C07.9. Parotid gland C08.0-C08.1, C08.8-C08.9. Submaxillary and sublingual glands
Oropharynx	C01.9. Base of the tongue C02.4. Lingual tonsil C05.1, C05.2. Soft palate + uvula C09.0-C09.1, C09.8. Palatine tonsils C10.0-C10.4, C10.8-C10.9. Oropharynx
Nasopharynx	C11.0-C11.3, C11.8-C11.9
Hypopharynx	C12.9. Pyriform sinus C13.0-C13.2, C13.8-C13.9. Hypopharynx

Pharynx NOS or overlapping*	C14.0, C14.2, C14.8
Sinonasal	C30. Nasal cavity C31.0-C31.3, C31.8-C31.9. Sinus
Larynx	C32.0-C32.3, C32.8-C32.9

NOS: Not otherwise specified. *Overlapping lesion of lip, oral cavity**,** and pharynx

All the tumours we selected fell within the ICD-O-3 morphological codes 8000/3-8711/3, excluding sarcomas and hematologic tumours (6). The codes' description is explained in *Annexes 3-12.*

In all instances, we segregated head and neck tumours by sex and age groups distributed into cohorts of 0-49, 50-59, 60-69, 70-79, and 80+ years. This facilitated a comparison of case distribution by sex and age. Additionally, we differentiated between the periods 1994-2001, 2002-2009, and 2010-2018 to better understand the distribution over the last decades and identify any inflection points in incidence.

7.5 STUDY PROCEDURES

7.5.1 DATABASE

The CRG and CRT serve as population-based cancer registries situated in the North-East and South of Catalonia, respectively. The CRG encompasses a population of 820,276 individuals in the province of Girona, while the CRT covers 855,769 people in the province of Tarragona, as reported by the Institut d'Estadística de Catalunya (IDESCAT) in November 2023 (95). Combined, they represent 20% of the population of Catalonia. Affiliated with the International Association of Cancer Registries (IACR) and the Spanish Network of Cancer Registries (Red Española de Registros del Cáncer - REDECAN)(96), both registries routinely contribute to the International Agency for Research in Cancer (IARC) monograph "Cancer Incidence in Five Continents" (97).

Their primary objective is to continuously identify and record all newly diagnosed cancer cases among residents of Girona and Tarragona provinces, regardless of the location of diagnosis.

Commencing in 1994 for CRG and 1980 for CRT, their activities involve meticulous data collection, processing, and the elaboration of results to determine the incidence, mortality, survival and prevalence of cancer, along with its distribution across various variables, as well as the evolution over time and the future estimation of these indicators. The registries also focus on monitoring temporal trends and estimating future indicators.

Both CRG and CRT adhere to international guidelines for population-based cancer registries (98), from the definition of cases to the systems of operation and elaboration of results, ensuring the consistency and comparability of data globally.

7.5.1.1 Information sources

Data on new incident cases of cancer are sourced from both public and private healthcare centres in the provinces of Girona and Tarragona. Additionally, information is collected from other public and private remote centres, often located in Barcelona, where some patients seek treatment either due to these centres being the reference points for their pathology or based on individual patient preferences. This data is extracted from various sources, including hospital discharges, haematology and pathology laboratories, and death certificates[1]. Subsequently, these data are meticulously processed to derive incidence rates, serving as foundational information for calculating various other epidemiological indicators.

Mortality information is derived from the Mortality Registry of Catalonia, compiled by the *Servei de Gestió i Anàlisi de la Informació* for the *Planificació Estratègica* of the *Direcció General de Recursos Sanitaris* of the Health Department of the *Generalitat de Catalunya*. Additionally, data is obtained from the *Índice Nacional de Defunciones* of the Spanish *Ministerio de Sanidad, Consumo y Bienestar Social*. The original mortality data, sourced from statistical death bulletins, not only facilitate the identification of cases not found in other sources but also enable the verification of existing registry information.

[1] Those cases in which the only information available is the death certificate and cannot be identified after exhaustive research by the registry personnel are classified as Death-Certificate-Only (DCO) cases. Those cases that were initially notified by death bulletin but were posteriorly identified after revision are classified as Death-Certificate Notification (DCN). In DCO cases, the incidence date is considered as the date of death. Therefore, the percentage of DCO gives insight on quality data of the registry (it is important it remains below 5-10%).

The information on the population of the provinces of Girona and Tarragona, stratified by sex and age group, is acquired from estimates and projections provided by IDESCAT (95).

7.5.1.2 Definition and Registration of Cases

Any invasive malignant tumor, in situ carcinoma, or tumor with uncertain behaviour diagnosed in a patient residing in the province of Girona and Tarragona at the time of diagnosis or at the time of death (in DCO/DCN cases) is classified as a case and is documented in the databases of the CRG and CRT. It's important to note that the recorded entities are tumours, not individuals, under the assumption that a single patient may have two or more tumours. Consequently, the incidence reflects the number of primary cancers, not the number of patients with cancer.

The registration guidelines and multiplicity criteria used adhere to those outlined in the International Rules for Multiple Primary Cancers of the IARC, the IACR, and the European Network of Cancer Registries (ENCR). For calculating and presenting the incidence results, the international standard criteria established in the joint recommendations of the ENCR, IARC, and IACR are employed (98).

To establish a case as a resident of the provinces of Girona or Tarragona, the CRG and the CRT utilize existing information from hospital databases and other facilities, along with archived medical records and death certificates. In case of discordance between different sources, the information is actively reviewed alongside the files in the medical records. If doubts persist, the place of residence is accepted according to the source of information considered to be the most reliable. A resident is recognized as any person who resided in the provinces of Girona or Tarragona for a period of at least 2 years prior to their cancer diagnosis.

All things considered, the CRG and the CRT record the following details for each case: demographic characteristics, pathology, localization and sub-localization according to the ICD-O-3 code (6), method and date of diagnosis, and date of death if applicable.

7.5.1.3 Data processing

Once the information is collected at the CRG and CRT, the data undergo preprocessing before analysis. Quality control checks are conducted to ensure consistency, completeness[2] of information, accurate coding, absence of duplication, and optimal accuracy, among other aspects related to its general quality.

Table 2. Quality indicators of head and neck tumours registered in GCR and TCG, Girona and Tarragona (1994-2018) *(99,100)*.

Quality indicators	
Histological verification (HV) [1]	97,3%
Death certificate only (DCO)	0,00%
Completeness	95,80%

[1] HV= percentage of registered cases with histological verification of the diagnosis. A low proportion suggests incomplete case coverage.

Confidentiality is strictly maintained throughout the entire process, in adherence to the provisions of the Data Protection European Union Directive 1995/46/EC and *Ley Orgánica 3/2018 de 5 de diciembre* concerning the guarantee of data protection (101) and done in alignment with the ethical principles laid out in the Declaration of Helsinki (102).

7.5.1.4 Time coverage

The CRG database has provided coverage since January 1994. Therefore, cases preceding this year are not included in our study, although the CRT has had coverage since January 1980. To gather comprehensive data on incidence, it's crucial to obtain information on new cases and mortality. It's important to recognize that there is always a time lag in acquiring this information, impacting our study period as well. Consequently, our study is limited to data up to December 2018, marking the latest month covered in the investigation.

It's worth mentioning that the database undergoes regular updates as the registry acquires more refined information. This may lead to slight variations in results across different

[2] Degree to which all cancer cases occurring in the covered territory are included in the registry database.

publications. For our study, we considered the most recent information to be of the highest quality available.

7.5.2 DATA COLLECTION

An anonymized database was elaborated with the selected incident study cases identified (overall HNC cases and HNC cases by subsite). Clinical and morphological characteristics were obtained from the CRG and CRT databases and collected for each case, mainly including demographical characteristics.

All data were handled in agreement with current confidentiality regulations inherent to the usual methodology of the CRG and the CRT. All data were stored guaranteeing its confidentiality, security, and authenticity. Under no circumstances the information collected included data that would have allowed the patient's identity to be known, as each patient was only identified by a numerical code. In order to ensure the confidentiality of the study data, only the coordinating investigator and the team of investigators, the promotor, the ethics committee, the competent health authorities, and the technicians responsible for data analysis had access to the data. The documents generated during the study and the database was protected against unauthorized use by people outside the study and were therefore considered strictly confidential. The processing, communication, and transfer of the personal data of all participating study cases complied with the ethical aspects mentioned in *Section 12* and the provisions clarified in *Section 7.5.1.3.*

7.6 VARIABLES

7.6.1 OUTCOME

- **Number of cases of HNC:** discrete quantitative variable presented as absolute frequencies and percentages during descriptive analyses, and as incidence rates estimated as crude rate (CR), age-standardized to the European standard population incidence rate ($ASIR_E$), age-standardized to the World standard population incidence rate ($ASIR_W$) and Age-specific rates (ASR) during incidence analyses; categorised as

overall head and neck, lip, oral cavity, oropharynx, nasopharynx, hypopharynx, pharynx (NOS), larynx, sinonasal and salivary glands.

7.6.2 INDEPENDENT VARIABLES

- **Age**: categorized as continuous quantitative variable measured in years when expressed in years at the moment of diagnosis, mean age (SD) and median age (IQR); and categorized as polytomous ordinal qualitative variable when expressed in 5 age groups (0-49; 50-59; 60-69; 70-79, 85+).
- **Sex**: categorized as dichotomous nominal qualitative variable defined as men or women.
- **Period**: categorized as polytomous ordinal qualitative variable divided in 3 groups (1994-2001; 2002-2009, 2010-2018).
- **Topography or subsite**: categorized as polytomous nominal qualitative variable.
- **Cancer registry**: categorized as dichotomous nominal qualitative variable defined as Girona or Tarragona.

7.7 STATISTICAL ANALYSIS

We performed a descriptive analysis and estimated the incidence rates and trends in incidence for overall HNC and by subsites.

Descriptive statistics have been expressed as median and interquartile range (IQR) or mean and standard deviation (SD) for quantitative variables, and as absolute frequencies and percentages for qualitative variables. The number of HNC cases was summarized using absolute frequencies and percentages. Descriptive tables compared men and women using chi-squared ($\chi 2$) or Fisher's exact test when low cell counts in the comparison of categorical variables, expressed as number (%). T-tests was utilized to compare sexes concerning continuous descriptive variables, expressed as mean (SD).

Incidence has been estimated as Crude Rate (CR)[3], Age-Standardized to the European population Incidence Rate ($ASIR_E$)[4], Age-Standardized to the WHO World population Incidence Rate ($ASIR_W$) and Age-specific rates. The population of the province of Girona was provided by the IDESCAT (95) to calculate the incidence rates. Age-standardized rates were calculated by stratifying the age into 18 groups of 5 years each using the 2013 European population for $ASIR_E$ and World Segi 1960 standard population for $ASIR_W$. Estimations were made with the direct method, as we had a large denominator (in our case the population of the provinces of Girona and Tarragona) and the frequency of events was not too reduced to get unstable rates. This method allowed to create comparable adjusted rates owing to the use of an identical standard population (in this case, the European and the World populations). We computed CR, $ASIR_E$, and $ASIR_W$ with the 95% Confidence Interval (CI) and results were expressed in 100.000 inhabitants per year. For further information regarding the calculation of rates, please refer to *Annex 2*.

The trends in the incidence have been assessed through the Annual Percent Change (APC) of ASR, which indicates the average annual variation in rates expressed as a percentage increase or decrease. The 95% confidence interval (95% CI) of the APC allowed us to evaluate the statistical significance or non-significance of the trend: if the CI contained 0, the trend was understood as statistically non-significant, whereas if the interval did not contain 0, it was considered that the trend increased (if the APC>0) or decreased (if the APC<0). To depict the incidence trends in the graphs, the Poisson model was employed, given its superior statistical fit to the distribution of cancer case incidence.

Statistical significance has been determined at p-value <0.05 for all analyses, defining a 95% confidence interval for all analyses. Analyses have been performed using R version 4.3.2 to examine relationships between variables.

[3] Crude Rate: number of incident cases of cancer during the study period divided by the population studied. It is expressed as a number per 100.000 inhabitants per year.
[4] Adjusted Rate: a fictious summary rate statistically adjusted to remove the effect of age, to permit unbiased comparison between populations having different age structures. They should be understood as the rates that would occur in another population with an age structure equal to that used as the standard.

8. RESULTS

8.1 DESCRIPTIVE ANALYSIS

A total number of 7,966 cases of HNC were identified in the GCR and TCR database from the period 1994-2018. Among these cases, 84% were men while only 16% were women. HNC was diagnosed at a mean age of 64 years for men and 67 for women, and 5.1 times more in men than in women. For men, cancer of the larynx was the most diagnosed subsite (38%), followed by cancer of the oral cavity (18%), and oropharyngeal cancer (15%). In women, oral cavity cancer was the most diagnosed malignancy accounting for 40% of all cases, followed by oropharyngeal cancer (12%), and salivary glands cancer (12%). For further information about descriptive epidemiology of HNC morphologies consult *Annexes 3-12*.

Table 3 summarizes demographic characteristics of HNC cases of the study population, stratified by sex. Age was divided in 5 groups and topographic site in 9 categories. There were significant differences between sexes for mean age, age groups and topographic site.

Table 3. Summary of the descriptive epidemiology stratified by sex, Girona and Tarragona (1994-2018).

	Men	**Women**	**Total**	**P-value** [1]
N (%)	6,667 (83.69)	1,299 (16.31)	7,966 (100)	
Mean age ± SD	63.50 ± 12.43	67.01 ± 15.49	64.07 ± 13.04	P<0.001
Median age (IQR)	63 (55-73)	68 (56-79)	64 (55-72)	
Age groups, years N (%)				P<0.001
0-49	892 (13,38)	179 (13,78)	1071 (13,44)	
50-59	1646 (24,69)	240 (18,48)	1886 (23,68)	
60-69	1949 (29,23)	259 (19,94)	2208 (27,72)	
70-79	1481 (22,21)	299 (23,02)	1780 (22,34)	
80+	699 (10,48)	322 (24,79)	1021 (12,82)	
Topographic site N (%)				P<0.001
Lip	823 (12,34)	149 (11,47)	972 (12,2)	
Oral Cavity	1173 (17,59)	522 (40,18)	1695 (21,28)	
Oropharynx	991 (14,86)	159 (12,24)	1150 (14,44)	
Nasopharynx	199 (2,98)	68 (5,23)	267 (3,35)	
Hypopharynx	591 (8,86)	32 (2,46)	623 (7,82)	
Pharynx (NOS)	56 (0,84)	7 (0,54)	63 (0,79)	
Larynx	2510 (37,65)	141 (10,85)	2651 (33,28)	
Sinonasal	146 (2,19)	65 (5)	211 (2,65)	
Salivary glands	178 (2,67)	156 (12,01)	334 (4,19)	
Cancer registry [2]				
Girona	3,067	613	3,680	
Tarragona	3,600	686	4,286	

N: absolute number of cases; SD: standard deviation; IQR: interquartile range; NOS: not otherwise specified.
[1] P value =T Student test for Mean age / Chi-square test for Age groups/ Fisher's Exact Test for Topographic sites
[2] Registry = Cancer registries from the populations of Girona and Tarragona, from which the data have been extracted.

Table 4 presents different HNC topographies stratified by sex and age groups. It demonstrates how the lowest mean age of diagnosis is attributed to oropharyngeal cancer cases for both men and women (53 and 54, respectively). It can be observed that the highest mean age of diagnosis is associated with lip cancer for both sexes (70 years in men and 78 in women).

The age distribution varies for each subsite and between sexes. Generally, men tend to present cancer at a younger age than women in most cases, except for not otherwise specified (NOS) pharyngeal cancer and laryngeal cancer, where most women present it between 50-59 years, and at a higher percentage than men. Nasopharyngeal cancer has the highest proportion of cases below 49 years for both sexes. In contrast, lip and salivary gland cancers have a higher proportion of cases over 85 years, especially in women. Statistical differences in the distribution of age groups by sex are evident in lip and oral cavity cancer, with men exhibiting a higher proportion of cases at younger ages than women.

Table 4. Descriptive epidemiology of Head and Neck Cancer subsites stratified by sex and age, Girona and Tarragona (1994-2018).

	Mean age ± SD	Age group, years N (%)					P-value [1]
		0-49	50-59	60-69	70-79	80+	
Lip							P<0.001
Men	70.84 ± 11.60	38 (4,62)	100 (12,15)	200 (24,3)	287 (34,87)	198 (24,06)	
Women	77.70 ± 9.95	2 (1,34)	4 (2,68)	20 (13,42)	54 (36,24)	69 (46,31)	
Oral cavity							P<0.001
Men	62.31 ± 12.77	184 (15,69)	294 (25,06)	344 (29,33)	251 (21,4)	100 (8,53)	
Women	68.77 ± 15.31	66 (12,64)	81 (15,52)	99 (18,97)	121 (23,18)	155 (29,69)	
Oropharynx							P=0.701
Men	60.54 ± 10.95	160 (16,15)	326 (32,9)	285 (28,76)	172 (17,36)	48 (4,84)	
Women	61.47 ± 13.06	23 (14,47)	52 (32,7)	45 (28,3)	27 (16,98)	12 (7,55)	
Nasopharynx							P=0.653
Men	52.90 ± 14.99	94 (47,24)	41 (20,6)	34 (17,09)	21 (10,55)	9 (4,52)	
Women	54.24 ± 17.26	26 (38,24)	15 (22,06)	13 (19,12)	9 (13,24)	5 (7,35)	
Hypopharynx							P=0.635
Men	61.15 ± 10.75	82 (13,87)	185 (31,3)	201 (34,01)	86 (14,55)	37 (6,26)	
Women	60.97 ± 13.58	7 (21,88)	9 (28,13)	9 (28,13)	4 (12,5)	3 (9,38)	
Pharynx NOS							P=0.511
Men	61.41 ± 12.58	8 (14,29)	20 (35,71)	13 (23,21)	10 (17,86)	5 (8,93)	
Women	58.14 ± 12.59	2 (28,57)	3 (42,86)	0 (0)	2 (28,57)	0 (0)	
Larynx							P=0.287
Men	63.71 ± 11.43	283 (11,27)	631 (25,14)	808 (32,19)	565 (22,51)	223 (8,88)	
Women	61.79 ± 11.44	21 (14,89)	43 (30,5)	41 (29,08)	27 (19,15)	9 (6,38)	
Sinonasal							P=0.159
Men	64.90 ± 14.30	27 (18,49)	20 (13,7)	37 (25,34)	38 (26,03)	24 (16,44)	
Women	69.98 ± 14.08	7 (10,77)	7 (10,77)	12 (18,46)	20 (30,77)	19 (29,23)	
Salivary glands							P=0.290
Men	70.17 ± 15.37	16 (8,99)	29 (16,29)	27 (15,17)	51 (28,65)	55 (30,9)	
Women	67.27 ± 17.84	25 (16,03)	26 (16,67)	20 (12,82)	35 (22,44)	50 (32,05)	

N: absolute number of cases; SD: standard deviation; NOS: not otherwise specified.
[1] P value= Chi-square for oral cavity, oropharynx, and salivary glands/ Fisher's Exact Test for lip, nasopharynx, hypopharynx, pharynx (NOS), larynx and sinonasal. To assess the statistical differences in the distribution of age groups by sex.

8.2 INCIDENCE RATES

Age-specific rates (ASR) of overall HNC can be observed in *Figure 3,* stratified by five-year groups. From the age of 40, the incidence increases substancially and it did not diminish in subsequent years. Nevertheless, from the age of 85, a sharp decline in the incidence of overall HNC is observed in our population, decreasing nearly by half.

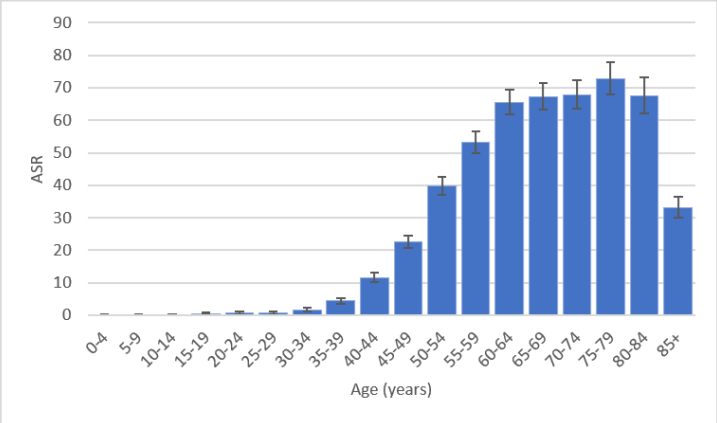


Figure 3. Age-specific rates (ASR) of overall head and neck cancer stratified by five-year groups, Girona and Tarragona (1994-2018). To review the data, refer to *Annex 13.*

Crude and adjusted incidence rates of overall HNC and by subsite in the period of 1994-2018 are presented in *Table 5*, stratified by sex. In our case series, the overall CR was 23.04 new cases per 100,000 inhabitants/year, and the $ASIR_E$, 25.62 new cases per 100,000 inhabitants/year. Differences between males and females were observed, which were more notable in age-standardized rates. If $ASIR_E$ is considered, overall HNC was 6 times more incident in men than in women, and if $ASIR_W$ is looked upon, the rates were 6.2 times higher in men.

Regarding to HNC subsites, the CR varies among different locations, as well as between sexes. In all topographies, incidence rates are significantly higher in men than in women, particularly when considering $ASIR_W$. The most profound difference between sexes is observed in hypopharyngeal cancer, where if $ASIR_E$ is considered, it is nearly 21 times more incident in men than in women. Continuing with the analyses of $ASIR_E$, significant differences between men and women are also evident in NOS pharyngeal cancer, which is nearly 10 times more incident in men than in women. Additionally, in the case of lip cancer, the incidence is 6.7 times higher too in men compared to women. The incidence rates that demonstrate the smallest disparity between sexes are observed in salivary glands, where the incidence is only 1.4 times higher in men than in women.

Table 5. Incidence rates of overall head and neck cancer and by subsite, stratified by sex, Girona and Tarragona (1994-2018).

Topographic site	Men				Women				Both sexes			
	N	CR (95% CI)	$ASIR_E$ (95% CI)	$ASIR_W$ (95% CI)	N	CR	$ASIR_E$ (95% CI)	$ASIR_W$ (95% CI)	N	CR	$ASIR_E$ (95% CI)	$ASIR_W$ (95% CI)
Overall head and neck	6,667	38.65 (37.73-39-59)	45.28 (44.19-46.38)	24.27 (23.66-24.89)	1,299	7.50 (7.09-7.92)	7.55 (7.13-7.98)	3.93 (3.69-4.18)	7,966	23.04 (22.53-23.55)	25.62 (25.06-26.19)	13.93 (13.60-14.26)
Lip	823	4.77 (4.45-5.11)	5.78 (5.39-6.19)	2.42 (2.24-2.60)	149	0.86 (0.73-1.01)	0.79 (0.66-0.93)	0.27 (0.22-0.33)	972	2.81 (2.64-2.99)	3.07 (2.88-3.27)	1.29 (1.20-1.39)
Oral Cavity	1,173	6.80 (6.42-7.20)	7.91 (7.46-8.37)	4.36 (4.11-4.63)	522	3.01 (2.76-3.28)	2.97 (2.71-3.24)	1.47 (1.32-1.62)	1,695	4.90 (4.67-5.14)	5.38 (5.13-5.65)	2.91 (2.76-3.06)
Oropharynx	991	5.74 (5.39-6.11)	6.65 (6.24-7.08)	3.87 (3.63-4.13)	159	0.92 (0.78-1.07)	1.00 (0.85-1.18)	0.60 (0.51-0.71)	1,150	3.33 (3.14-3.52)	3.76 (3.54-3.98)	2.23 (2.09-2.36)
Nasopharynx	199	1.15 (1.00-1.33)	1.21 (1.05-1.40)	0.85 (0.73-0.98)	68	0.39 (0.30-0.50)	0.41 (0.32-0.52)	0.29 (0.22-0.38)	267	0.77 (0.68-0.87)	0.81 (0.71-0.91)	0.57 (0.50-0.65)
Hypopharynx	591	3.43 (3.16-3.71)	3.98 (3.67-4.32)	2.32 (2.13-2.52)	32	0.18 (0.13-0.26)	0.19 (0.13-0.28)	0.12 (0.08-0.17)	623	1.80 (1.66-1.95)	2.04 (1.88-2.21)	1.21 (1.11-1.31)
Pharynx NOS	56	0.32 (0.25-0.42)	0.37 (0.28-0.48)	0.21 (0.16-0.28)	7	0.04 (0.02-0.08)	0.04 (0.02-0.09)	0.03 (0.01-0.06)	63	0.18 (0.14-0.23)	0.20 (0.15-0.26)	0.12 (0.09-0.15)
Larynx	2,510	14.55 (13.99-15.13)	17.17 (16.50-17.86)	9.23 (8.85-9.61)	141	0.81 (0.68-0.96)	0.90 (0.75-1.06)	0.53 (0.44-0.63)	2,651	7.67 (7.38-7.96)	8.69 (8.36-9.02)	4.80 (4.61-4.99)
Sinonasal	146	0.85 (0.71-1.00)	0.98 (0.83-1.16)	0.49 (0.41-0.59)	65	0.38 (0.29-0.48)	0.37 (0.28-0.47)	0.17 (0.12-0.22)	211	0.61 (0.53-0.70)	0.66 (0.57-0.76)	0.33 (0.28-0.38)
Salivary glands	178	1.03 (0.89-1.20)	1.21 (1.04-1.41)	0.52 (0.43-0.61)	156	0.90 (0.76-1.05)	0.87 (0.74-1.03)	0.45 (0.37-0.55)	334	0.97 (0.87-1.08)	1.01 (0.90-1.13)	0.48 (0.42-0.54)

Rates per 100,000 inhabitants per year. N: absolute number of cases; CR: crude rate; CI: confidence interval; $ASIR_E$: age-standardized incidence rate to the European population; $ASIR_W$: age-standardized incidence rate to the World population; NOS: not otherwise specified.

8.3 TRENDS IN INCIDENCE

Over the entire period from 1994 to 2018, incidence rates have shown variations in most head and neck cancer cases, affecting both men and women. *Table 6* provides a summary of the incidence rates (CR, $ASIR_E$, and $ASIR_W$) for overall head and neck cancer and by subsite, categorized into three time periods. This allows to observe the changing trends in incidence rates over time.

For better understanding, *Table 7* displays the Annual Percentage of Change (APC) with a 95% confidence interval (95% CI) for both overall head and neck cancer incidence and specific topographies. The p-value indicates whether the change has been statistically significant.

Over the entire period from 1994 to 2018, HNC incidence has significantly decreased for both sexes, with an APC of -1.83. This decline is attributed to the statistically significant decrease observed in men, contrary to what has happened with women, who have significantly increased their incidence rates during the study period.

A similar pattern emerges for hypopharyngeal and laryngeal cancer. Both have experienced a significant decrease in total incidence, driven by a statistically significant decrease in men, in contrast to a statistically significant increase in incidence among women during the study period.

Two other topographies that have significantly decreased their total incidence are lip cancer and salivary gland cancer. These have decreased their incidence in both men and women, with the decline being statistically significant only for men. Lip cancer has experienced the most pronounced decrease, achieving an APC of -5.34, particularly driven by men with an APC of -6.27. Similarly, though not statistically significant, sinonasal cancer has decreased its total incidence and incidence for both men and women.

Oral cavity cancer, nasopharyngeal cancer, and pharyngeal NOS cancer have all experienced a statistically nonsignificant decrease in incidence during the study period. In the case of oral cavity cancer, men significantly increased their incidence, while women significantly decreased it. For nasopharyngeal cancer, the only statistically significant change was the

decrease in incidence among men. No significant trend changes were observed in pharyngeal cancer.

Something different happens with oropharyngeal cancer. This is the only cancer that shows a nonsignificant increase in total incidence with an APC of 0.18 during the study period. In this case, the incidence among women significantly increases with an APC of 6.03, while the incidence among men decreases non-significantly.

All these changes in incidence are reflected in *Figure 4.* It illustrates the trends in total incidence and the incidence trends for men and women overall HNC, as well as for each of its subsites, accompanied by the corresponding APC data.

Table 6. Incidence rates of overall head and neck cancer and by subsite, stratified by time period, Girona and Tarragona (1994-2018).

Topographic site	Period											
	1994-2001				2002-2009				2010-2018			
	N	CR (95% CI)	$ASIR_E$ (95% CI)	$ASIR_W$ (95% CI)	N	CR (95% CI)	$ASIR_E$ (95% CI)	$ASIR_W$ (95% CI)	N	CR (95% CI)	$ASIR_E$ (95% CI)	$ASIR_W$ (95% CI)
Overall head and neck	2,399	26.55 (25.50-27.63)	30.73 (29.51-32.00)	17.04 (16.32-17.78)	2,545	22.57 (21.70-23.46)	25.87 (24.87-26.91)	14.15 (13.56-14.75)	3,022	21.19 (20.44-21.96)	22.75 (21.93-23.59)	12.07 (11.61-12.55)
Lip	369	4.08 (3.68-4.52)	4.78 (4.30-5.30)	2.13 (1.90-2.38)	341	3.02 (2.71-3.36)	3.39 (3.04-3.78)	1.40 (1.23-1.57)	262	1.84 (1.62-2.07)	1.85 (1.63-2.10)	0.71 (0.61-0.82)
Oral cavity	447	4.95 (4.50-5.43)	5.70 (5.18-6.26)	3.18 (2.87-3.51)	537	4.76 (4.37-5.18)	5.38 (4.93-5.86)	2.93 (2.67-3.21)	711	4.98 (4.62-5.36)	5.26 (4.87-5.67)	2.75 (2.53-2.98)
Oropharynx	280	3.10 (2.75-3.48)	3.57 (3.16-4.02)	2.20 (1.94-2.48)	367	3.25 (2.93-3.60)	3.82 (3.44-4.23)	2.25 (2.02-2.50)	503	3.53 (3.22-3.85)	3.88 (3.55-4.24)	2.26 (2.06-2.48)
Nasopharynx	83	0.92 (0.73-1.14)	1.00 (0.80-1.24)	0.70 (0.55-0.87)	84	0.74 (0.59-0.92)	0.81 (0.65-1.01)	0.56 (0.44-0.71)	100	0.70 (0.57-0.85)	0.71 (0.57-0.86)	0.52 (0.42-0.65)
Hypopharynx	206	2.28 (1.98-2.61)	2.65 (2.30-3.04)	1.65 (1.42-1.90)	213	1.89 (1.64-2.16)	2.23 (1.94-2.55)	1.34 (1.16-1.54)	204	1.43 (1.24-1.64)	1.56 (1.36-1.80)	0.86 (0.74-1.00)
Pharynx NOS	19	0.21 (0.13-0.33)	0.24 (0.15-0.38)	0.16 (0.10-0.25)	19	0.17 (0.10-0.26)	0.18 (0.11-0.29)	0.11 (0.07-0.18)	25	0.18 (0.11-0.26)	0.19 (0.12-0.29)	0.10 (0.06-0.15)
Larynx	838	9.27 (8.66-9.92)	10.76 (10.04-11.51)	6.09 (5.67-6.54)	814	7.22 (6.73-7.73)	8.47 (7.89-9.08)	4.77 (4.43-5.13)	999	7.00 (6.58-7.45)	7.72 (7.24-8.22)	4.09 (3.82-4.36)
Sinonasal	59	0.65 (0.50-0.84)	0.75 (0.57-0.97)	0.37 (0.28-0.49)	59	0.52 (0.40-0.67)	0.55 (0.42-0.72)	0.28 (0.21-0.37)	93	0.65 (0.53-0.80)	0.69 (0.55-0.85)	0.34 (0.26-0.42)
Salivary glands	98	1.08 (0.88-1.32)	1.28 (1.04-1.56)	0.56 (0.44-0.70)	111	0.98 (0.81-1.19)	1.04 (0.86-1.26)	0.50 (0.40-0.62)	125	0.88 (0.73-1.04)	0.89 (0.73-1.06)	0.44 (0.34-0.54)

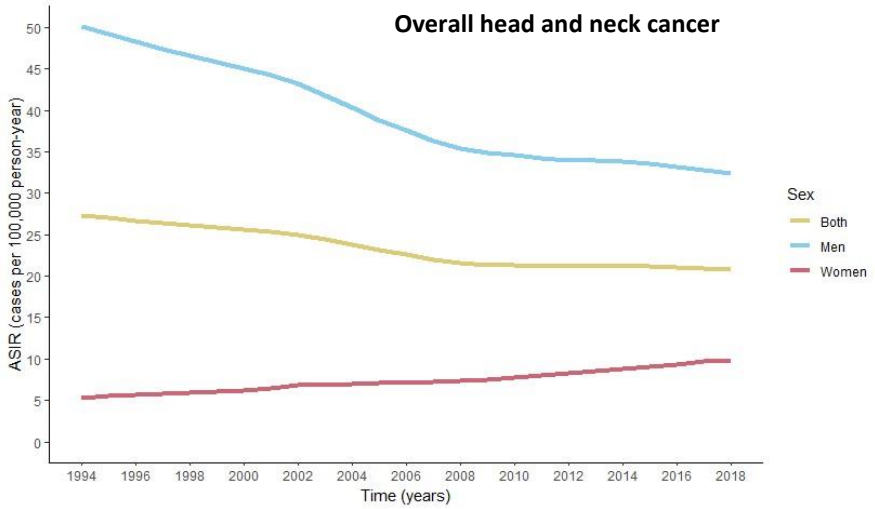
Rates per 100,000 inhabitants per year. N: absolute number of cases; CR: crude rate; CI: confidence interval; $ASIR_E$: age-standardized incidence rate to the European population; $ASIR_W$: age-standardized incidence rate to the World population; APC: annual percentage of change; NOS: not otherwise specified.

Table 7. Number of cases (N) and annual percent of change (APC) in incidence rates stratified by sex, Girona and Tarragona (1994-2018).

Topographic site	Men			Women			Both sexes		
	N	APC (95% CI)	P value	N	APC (95% CI)	P value	N	APC (95% CI)	P value
Overall head and neck	6,667	**-2.63** (-2.96; -2.29)	<0.01	1,299	**1.77** (0.97;2.56)	<0.01	7,966	**-1.83** (-2.14; -1.52)	<0.01
Lip	823	**-6.27** (-7.25; -5.29)	<0.01	149	-1.18 (-3.49;1.13)	0.32	972	**-5.34** (-6.24; -4.45)	<0.01
Oral cavity	1,173	**-1.62** (-2.42; -0.82)	<0.01	522	**1.84** (0.59;3.09)	<0.01	1,695	-0.54 (-1.21;0.13)	0.11
Oropharynx	991	-0.78 (-1.65;0.09)	0.08	159	**6.03** (3.63;8.42)	<0.01	1,150	0.18 (-0.64;0.99)	0.67
Nasopharynx	199	**-3.19** (-5.14; -1.23)	<0.01	68	1.29 (-2.1;4.69)	0.46	267	-2.01 (-3.7; -0.33)	0.02
Hypopharynx	591	**-3.71** (-4.84; -2.59)	<0.01	32	**5.73** (0.36;11.11)	0.04	623	**-3.15** (-4.25; -2.06)	<0.01
Pharynx NOS	56	-2.07 (-5.76;1.61)	0.27	7	2.82 (-8.03;13.68)	0.61	63	-1.46 (-4.93;2.02)	0.41
Larynx	2,510	**-2.48** (-3.02; -1.93)	<0.01	141	**4.85** (2.36;7.33)	<0.01	2,651	**-1.97** (-2.5; -1.44)	<0.01
Sinonasal	146	-0.06 (-2.36;2.24)	0.96	65	-1.03 (-4.5;2.44)	0.56	211	-0.27 (-2.19;1.64)	0.78
Salivary glands	178	**-2.78** (-4.87; -0.69)	<0.01	156	-1.69 (-3.92;0.55)	0.14	334	**-2.22** (-3.75; -0.7)	<0.01

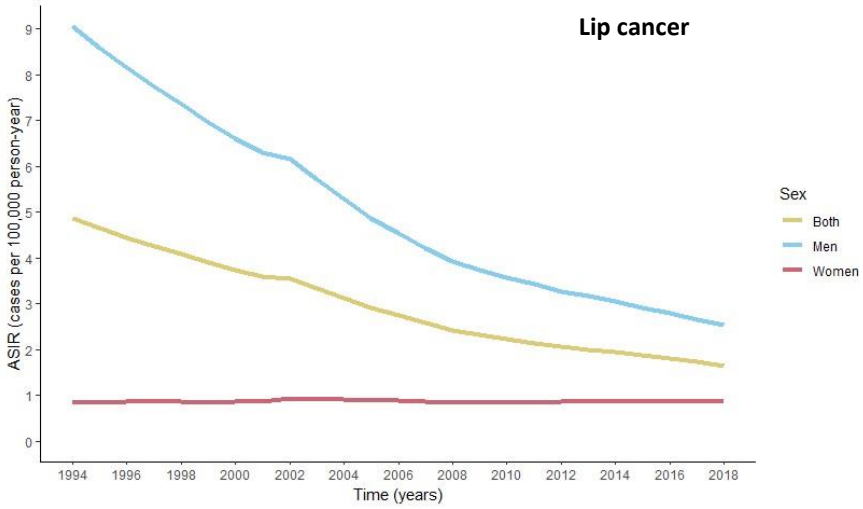
N: absolute number of cases; APC: annual percentage of change; CI: confidence interval; NOS: not otherwise specified.

Overall head and neck cancer



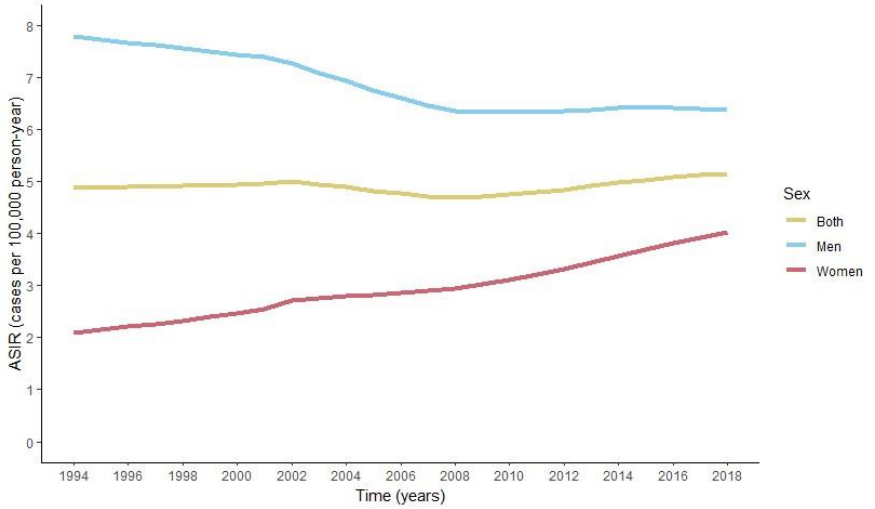
APC both: -1.83 (95% CI -2.14; -1.52)
APC men: -2.63 (95% CI -2.96; -2.29)
APC women: 1.77 (95% CI 0.97; 2.56)

Lip cancer



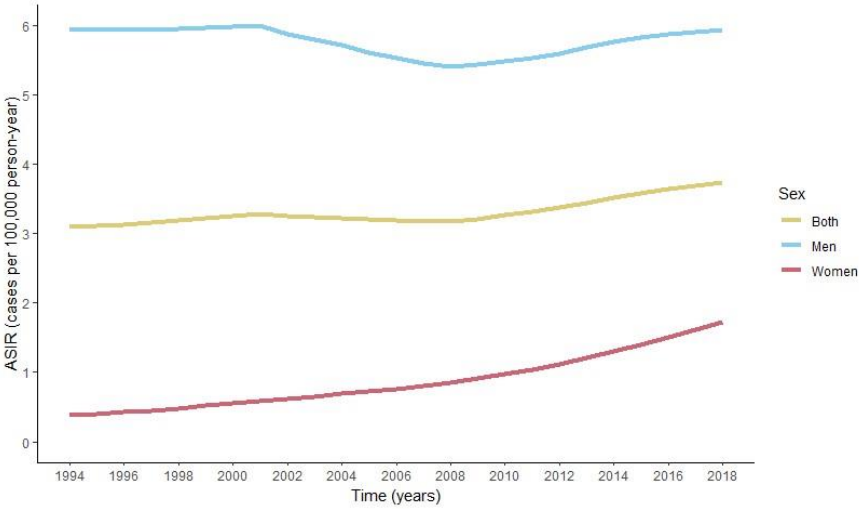
APC both: -5.34 (95% CI -6.24; -4.45)
APC men: -6.27 (95% CI -7.25; -5.29)
APC women: -1.18 (-3.49; 1.13)

Oral cavity cancer



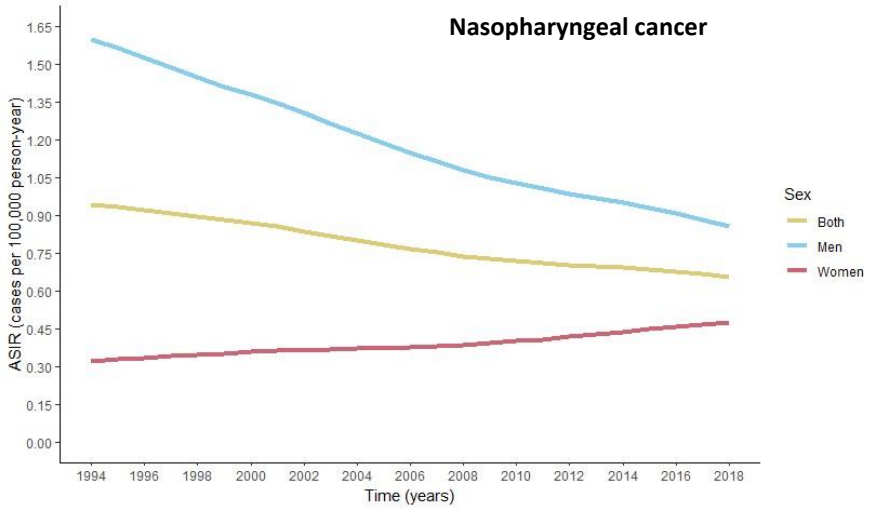
APC both: -0.54 (95% CI -1.21; 0.13)
APC men: -1.62 (95% CI -2.42; -0.82)
APC women: 1.84 (0.59; 3.09)

Oropharyngeal cancer



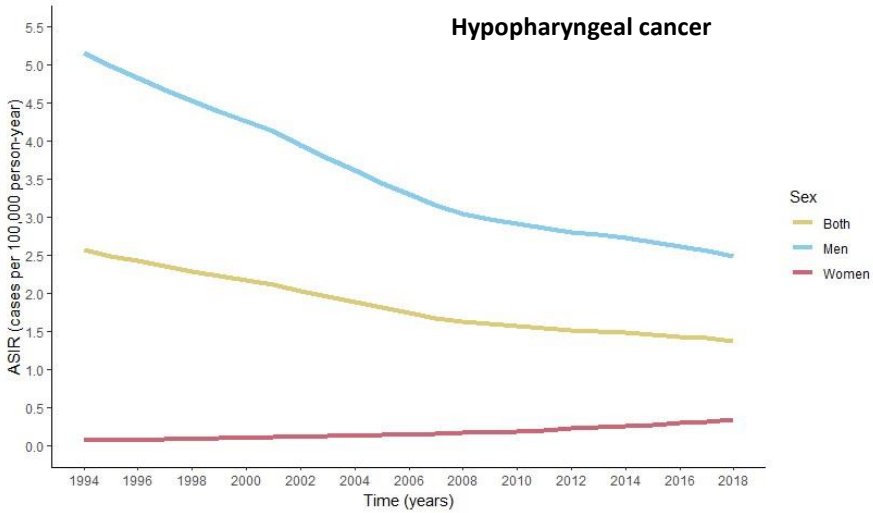
APC both: 0.18 (95% CI -0.64; 0.99)
APC men: -0.78 (95% CI -1.65; 0.09)
APC women: 6.03 (3.63; 8.42)

Nasopharyngeal cancer



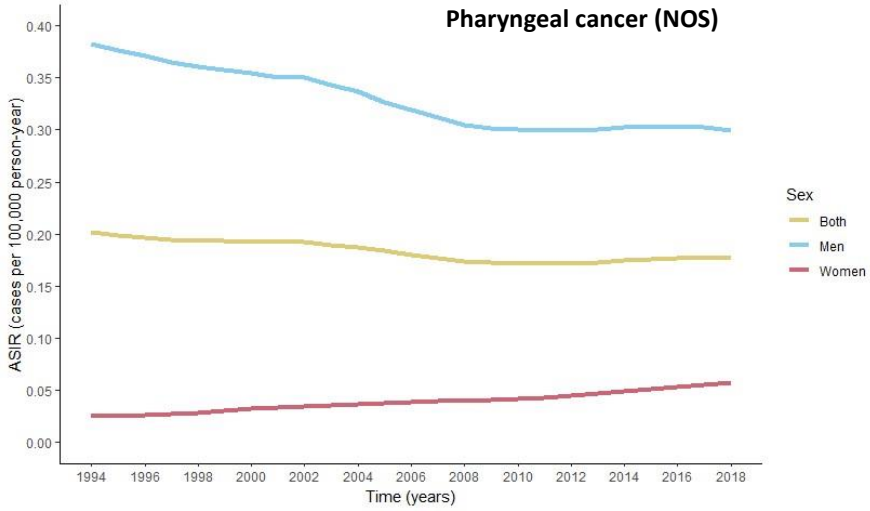
APC both: -2.01 (95% CI -3.7; -0.33)
APC men: -3.19 (95% CI -5.14; -1.23)
APC women: 1.29 (-2.1; 4.69)

Hypopharyngeal cancer



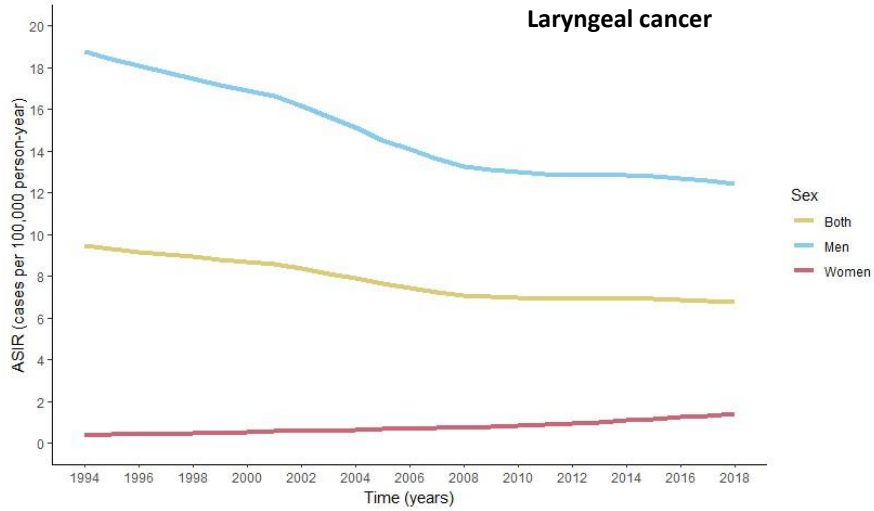
APC both: -3.15 (95% CI -4.25; -2.06)
APC men: -3.71 (95% CI -4.84; -2.59)
APC women: 5.73 (0.36; 11.11)

Pharyngeal cancer (NOS)

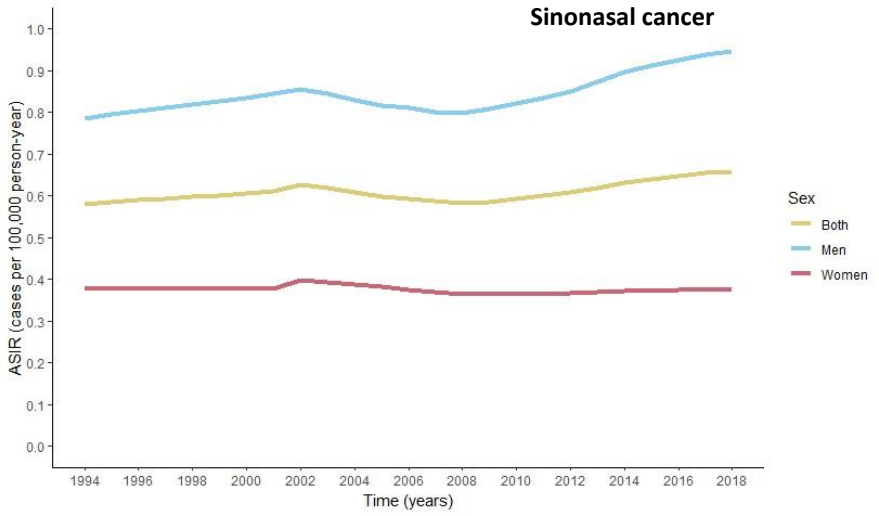


APC both: -1.46 (95% CI -4.93; 2.02)
APC men: -2.07 (95% CI -5.76; 1.61)
APC women: 2.82 (-8.03; 13.68)

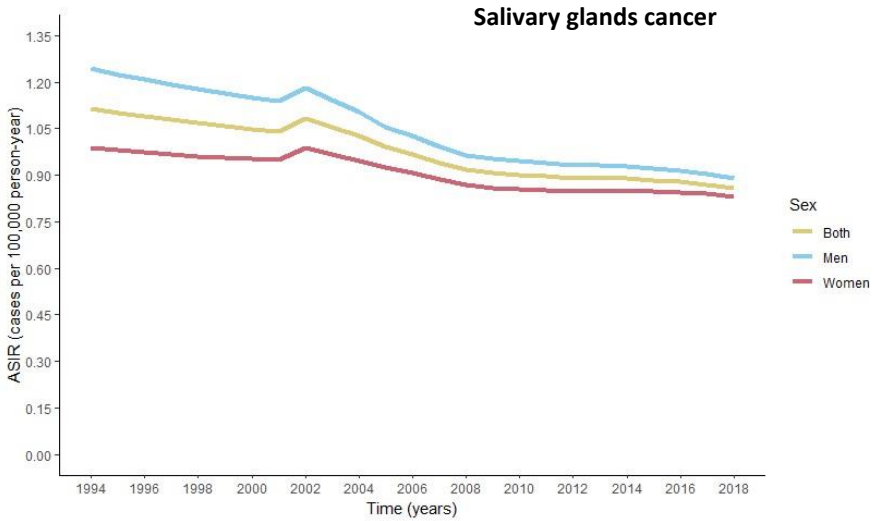
Laryngeal cancer



APC both: -1.97 (95% CI -2.5; -1.44)
APC men: -2.48 (95% CI -3.02; -1.93)
APC women: 4.85 (2.36; 7.33)



APC both: -0.27 (95% CI -2.19; 1.64)
APC men: -0.06 (95% CI -2.36; 2.24)
APC women: -1.03 (-4.5; 2.44)



APC both: -2.22 (95% CI -3.75; -0.7)
APC men: -2.78 (95% CI -4.87; -0.69)
APC women: -1.69 (-3.92; 0.55)

Figure 4. Trends in incidence and annual percent of change (APC) of overall head and neck cancer and by subsite, Girona and Tarragona (1994-2018).

9. DISCUSSION

In this retrospective study, we examined trends in HNC incidence and site-specific HNC incidence in the population of the provinces of Girona and Tarragona between 1994 and 2018. We observed a statistically significant decrease in the incidence of overall HNC from 1994 to 2018. By subsite, significant decreasing trends were observed for cancers of the lip, hypopharynx, larynx and salivary glands. In parallel, a non-significant decrease for the oral cavity, nasopharyngeal, pharyngeal NOS and sinonasal cancers were detected, while an increasing trend was observed for oropharyngeal cancer, although it did not reach statistical significance.

9.1 OVERALL HEAD AND NECK CANCER

With regard to overall HNC, over 80% were diagnosed in men and nearly 63% of those diagnosed with HNC were 60 and older, reporting a mean age at diagnosis of 64 years. This demographic distribution is consistent with findings from other studies in Europe. For instance, a study from the UK reported that more than two-thirds of all HNC patients were in the 60+ year age group (103). Similarly, a study in Germany reported a comparable age at diagnosis, with 50% of HNC patients being aged 60-79 years (104), while a study in the United States reported a mean age at diagnosis of 64 years (105).

An important sex difference was observed in the distribution of overall HNC cases, with a male-to-female ratio of 5.1. This sex disparity persisted across all age groups; however, the proportion of women affected increased in the older age categories, likely due to a larger female population within these categories.

The lower incidence of HNC observed in women compared with men, a pattern noted in many other studies, could be explained by differences in tobacco and alcohol consumption patterns. Tobacco (both smoked and smokeless) is a major and well-established contributor to HNC, according to the IARC (44,106), accounting for an estimated 75% of lip, oral cavity, and pharyngeal cancers in Western Europe (34). Smokeless tobacco products are also associated with an increased risk of HNC, particularly oral cavity cancer (OCC) (107). More frequently, HNC occurs when both alcohol and tobacco are used in combination, explaining 85% of

hypopharyngeal and laryngeal cancers, 75% of non-HPV-related OPC, and 61% of oral cavity cancers (108). Worldwide, tobacco or alcohol was attributed to 72% (95% CI 61% to 79%) of HNC cases, of which 35% were due to tobacco and alcohol combined.

As previously mentioned, a statistically significant decrease in the incidence of overall HNC was observed from 1994 to 2018, with an APC of -1.83, primarily driven by a statistically significant decrease in incidence among men with an APC of -2.63. Conversely, we observed an increasing trend among women, with an APC of 1.77. These findings align with numerous studies indicating that, in recent decades, the number of cases of HNC has been decreasing in men but increasing in women due to changes in habits and lifestyle. Therefore, the epidemiological trends observed in our population may be attributed to a shift in HNC risk factor exposure. The increase in HNC incidence among women could be explained by the rising prevalence of smoking among women. While female exposure to smoking has historically been lower than in men, the prevalence of smoking has increased in recent decades, explaining the upward trend in incidence in several countries worldwide. The stronger increase in incidence among women than in men has also been reported by others and is often attributed to the fact that women started smoking later than men (109,110). The impact of cigarette smoking on the historical trends of HNC is seen in the similarity with trends in lung cancer incidence two decades on; where lung cancer rates continue to decrease in males but increase in females in several European countries, coinciding with time-lagged tobacco consumption (111). This trend is also reflected in all HNC tobacco-related subsites, mainly involving the oral cavity, larynx, and hypopharynx.

There is a geographical variation in incidence for tobacco related tumours. Southern Europe has recorded the highest incidence rates (IRs) for epithelial tumours of the nasopharynx and larynx, a finding congruent with our own results, wherein the larynx emerges as the most prominently affected subsite. Meanwhile, Central Europe exhibits the highest IRs for epithelial tumours affecting the oral cavity, hypopharynx, and oropharynx. In contrast, the IRs for epithelial tumours of the oral cavity, oropharynx, larynx, and hypopharynx are comparatively lower in the United Kingdom, Ireland, and Northern Europe (112). Disparities in geographic incidence, as well as variations between sexes, may find explication in dissimilarities in risk factors prevalent among the two sexes.

9.2 OROPHARYNGEAL CANCER

By subsite, oropharyngeal cancer showed an upward trend (APC 0.18). A significant increase was observed in women (APC 6.03), meanwhile a non-significant decrease was observed in men (APC -0.78).

This specific trend of oropharyngeal cancer could also be explained by another important shift in HNC risk factors, in which tobacco and alcohol use have been declining in importance at the expense of oral HPV infection. We can see this reflected in regions with successful tobacco control programs, such as the United States, Australia, Denmark, and Canada, where the incidence of traditionally tobacco-associated head and neck cancers has experienced a decline (113). Furthermore, Spain, as evidenced by the Spanish National Health Survey (SNHS), has witnessed a reduction in tobacco consumption, with the prevalence of daily smoking among Spaniards decreasing from 34% in 1995 to 24% in 2011 (114). Stringent tobacco regulations introduced in 2010, coupled with intensified public health campaigns, have further decreased tobacco use to 20% at present, especially evident among men.

This temporal variability in the prevalence of the traditional HNC risk factor potentially explains the diminishment of overall HNC cases observed in our study, particularly among men, driven by a reduction in lip, oral, nasopharyngeal, hypopharyngeal and laryngeal cancers. Additionally, a population-based study describing cancer incidence trends in Catalonia from 1993 to 2007 revealed a rising trend of oral cavity and pharyngeal cancers among women, contrasting with a stable trend among men (115). This sex-specific disparity is postulated to be linked to a higher and earlier rate of smoking cessation among men compared to women. These findings align with the outcomes of our study, where a declining trend in tobacco-related cancers is evident in men, while an increasing trend is observed in women.

Simultaneously, the incidence of oropharyngeal carcinoma has been on the rise, attributed to a growing subgroup of HPV-positive. Additionally, in numerous Western countries, HPV-associated OPC incidence has increased by up to 225% within the last three decades, surpassing cervical cancer as the most prevalent HPV-linked cancer. Projections for the next 20 years anticipate that the majority of HNC will be HPV-positive, with estimates suggesting

that in certain European countries, such as the UK, OPC incidence will surpass that of OCC (62,67).

Some studies indicate that HPV prevalence in OPC has started to sharply increase in the most recent years in our setting. These results, together with our findings of increasing trends of OPC in our study population, especially among women, suggest that HPV-related OPC has started to rise, similar to what happened two decades ago in regions where most OPC cases are currently associated with HPV. However, growing evidence is showing that HPV infection, predominantly type 16 (HPV16), is causally related with a subset of OPC, particularly in younger age groups (116). The correlation between HPV infection and HNC development is strongest for OPC and weakest for oral cavity and laryngeal cancers. Unfortunately, we could not directly evaluate the association between OPC cases and HPV infection-related factors because information on HPV infection was not available in this study.

However, it is well-known that individuals with HPV-positive HNC tend to be younger, with an age difference ranging from 3 to 5 years. They also exhibit distinct risk factors associated with sexual behaviour, such as a higher number of lifetime sexual partners, earlier onset of sexual activity, engagement in premarital sex, and the practice of oral sex. Furthermore, this population is less likely to have a history of extensive tobacco and alcohol use (117). This observation may explain the higher proportion of oropharyngeal cancer cases within the age group of 50-59 years in our study, constituting 30% of the cases. In contrast, the majority of other subsites exhibit a higher proportion of cases among individuals aged 60 years or older.

Some studies also indicate that HPV is more prevalent in men than in women. Sex disparities in prevalence and rate changes are difficult to elucidate but may be linked to differences in sexual practices, given that over 90% of oral HPV infections are sexually acquired (118). HNC associated with smoking and alcohol consumption has been decreasing in incidence in recent decades, particularly among men, due to the substantial reduction in the prevalence of tobacco and alcohol consumption. Conversely, the incidence of HPV-positive OPC has been exponentially rising during the same period, predominantly among younger individuals in North America and Europe, reaching up to 2.5 times that of HPV-negative OPC (119). This increasing trend likely reflects the latency period of about 10 to 30 years after the onset of

changes in sexual behaviours relevant to oral HPV exposure. Indeed, sexual behaviour greatly varies across regions, with proportions of individuals reporting ever having oral sex exceeding 65% in the United States compared to less than 20% in countries in Southern Europe, such as Spain (60). This aligns with studies suggesting that HPV-related OPC has begun to increase in our setting approximately 20 years later than in other countries, such as the United States (67). This two-decade gap corresponds with temporal differences in smoking decline between the United States and Spain. This discrepancy might explain the substantial increase in oropharyngeal cancer in the United States in recent years compared to our study, where the trend is increasing but not significantly. Nevertheless, we anticipate that this trend will continue to rise in the coming decades due to the increase in Human HPV-related OPC.

We hypothesize that while oropharyngeal cancer related to alcohol and tobacco consumption may decrease, particularly among men, this reduction may be counterbalanced by an increase in oropharyngeal cancer cases in women associated with alcohol and tobacco consumption. Furthermore, considering prevalence estimates and the temporal lag in HPV prevalence, it is expected that the overall oropharyngeal cancer attributable to HPV, in both men and women, surpass the number of tobacco-related head and neck cancers in the coming years. However, it is still unclear whether tobacco and/or alcohol use can act as co-factors and/or effect modifiers in the risk of developing HPV-related OPC. Therefore, we cannot rule out the possibility that smoking is associated with an increased risk of HPV-positive OPC, as observed in previous studies in the US (120).

9.3 LIP CANCER

Among subsites, lip cancer has demonstrated a general decrease in its incidence over the study period with, a significant APC of -5.34. This decreasing trend was especially pronounced in men, while the trend in women remained stable. This is consistent with numerous studies which showed that in the majority of registry populations examined, lip cancer incidence rates have been in steady decline, particularly among men, in countries with predominantly European populations such as Austria, Denmark, and Poland/Kielce (21). Although rates in women are subject to less stability given fewer cases, rates appear to be rather stable or

slightly decreasing. Furthermore, the elevated incidence in Australian populations has been reported previously, and the aetiology of lip cancer is reasonably well understood. An elevated risk is predominantly linked to outdoor occupations, including the fishing industry and farming, as well as being resident in rural regions. The key causative factor is exposure to solar radiation (UVR), with Actinic Cheilitis, for example, considered a potential premalignant lesion caused by chronic sunlight exposure. The lower incidence among women has been partially attributed to use of lipstick, which in theory would protect users against sunlight exposure. Our results indicate that the incidence rates of lip cancer have either decreased or remained stable in our registry area over the last 24 years. The observed patterns in Australia, the U.S., and several European countries, including Spain, are likely explained by a declining number of the working population in outdoor occupations, possibly coupled with increases in primary prevention of solar radiation by outdoor workers, through sunscreen use and protective clothing and headwear. Furthermore, existing evidence linking tobacco smoking, especially with pipes, to lip and oral cavity cancer may also contribute to the observed trends, given the decreasing prevalence of smoking in recent decades, especially in men (121).

9.4 ORAL CAVITY CANCER

Alongside these results, we identified a slightly decreasing trend in incidence of oral cavity cancer. This decline is emphasized by a statistically significant decrease in incidence among men. Conversely, we observed an upward trend in incidence among women. Trends in oral cancer appear to be in decline in most of male populations, whereas rising incidence is commonly observed among females. The trends in rates are consistent with the global patterns and trends in tobacco and alcohol consumption, emphasizing the causal role of smoking and smokeless tobacco consumption in the occurrence of oral cancers.

The temporal patterns of oral cancer incidence reveal two contrasting patterns between sexes. Among men, decreasing trends are exhibited in the majority of registry populations of US, as well as in several European countries, including Spain, Italy, France and Switzerland. This is also consistent with our findings. Conversely, among women, rising rates are observed across various populations, notably in Spain, Poland/Kielce, Denmark, Slovenia, Estonia, Slovakia, the U.K., and Japan. The highest incidence rates persist in South and Central Asia,

along with selected countries and territories in the Pacific (21). It is noteworthy that many of the countries exhibiting increasing trends are categorized as developing countries, where tobacco and alcohol consumption continue to rise.

As previously mentioned, both tobacco and alcohol consumption are firmly established as risk factors for oral cancer. The association between oral cancer and alcohol consumption is particularly robust, even at moderate doses. Consequently, the incidence of oral and pharyngeal cancers in males has shown more favourable trends in countries located in southern Europe, where the prevalence of alcohol consumption has markedly declined since the late 1970s. A comprehensive study revealed that the odds ratios for head and neck cancer attributed to smoking, alcohol consumption, and betel quid chewing were 1.58, 8.23, and 2.29, respectively. Moreover, individuals engaging in all three habits exhibited a remarkably higher odds ratio of 20.6 for head and neck cancer compared to those with either one or two of these habits (38). In developed countries, the occurrence of OCC is infrequent among individuals who neither smoke nor consume alcohol. This pattern may elucidate the disparities in the observed trends between men and women, both in our study and globally.

On the contrary, recent epidemiological trends in the incidence of OCC in the United States suggest a potential shift in aetiology, characterized by an increasing number of younger patients who lack established risk factors, such as tobacco use and alcohol consumption. As tobacco use has diminished in the United States, leading to a decrease in the incidence of many tobacco-related cancers, researchers have proposed that the increase in oral cavity cancer may be attributed to anatomic sites with specific cell types in which HPV DNA is frequently identified. This observation highlights the importance of further investigating the role of HPV in oral cavity cancer, as it may potentially contribute to the development of this disease.

9.5 HYPOPHARYNGEAL AND LARYNGEAL CANCER

Regarding other tobacco and alcohol related HNC subsites, we observed a clear decline in the incidence trends of hypopharyngeal and laryngeal cancers. The overall decreasing trend in these two subsites is primarily driven by a marked reduction in the incidence trends among

men. Conversely, contrary to the male trends, there is a significant increase in the incidence trends of these two cancers among women. In our study, a decreasing trend in incidence was noted among men, with similar trends found in France, Italy, China, and England. The available evidence suggests that this decline in incidence is likely associated with a reduced consumption of tobacco in these populations, particularly given the reported decrease in incidence of other cancers directly linked to smoking, such as lung cancer, as mentioned earlier. The male-to-female ratio for hypopharyngeal and laryngeal cancers in our population is the highest among all subsites, with ratios of 19:1 and 18:1, respectively. This discrepancy can be attributed to the pronounced disparity in exposure to risk factors between sexes. Hypopharyngeal cancer is anatomically related to the larynx and exposed to similar risks factors. The incidence of laryngeal cancer strongly correlates with smoking trends, while hypopharyngeal cancer exhibits a stronger association with alcohol consumption, a plausible connection considering the anatomical site.

According to the most recent global data on laryngeal cancer, Spain exhibits the one of the highest age-standardized incidence rates among men worldwide. High rates were also found in Southeast Europe (France and Italy), Eastern European countries (Serbia and Poland), Latin America (Brazil and Argentina) and West Asia (Pakistan and Turkey) (122).

The incidence rates of laryngeal cancer in Spanish women have historically been low and rank among the lowest in Europe. However, a notable increase in incidence has been observed over the past decade, which is corroborated by studies on the prevalence of smoking in Spain that reported results in the same direction. This demonstrates the failure of public policies affecting females. The results of the SNHS showed that prevalence of smoking decreased in men and increased in women in recent decades. The traditional sex difference in smoking prevalence narrowed. There was an increase in the prevalence of women-smokers (especially in younger age groups) accompanied by a decrease in prevalence in the male population. Such trends suggest that in the near future there will be no sex differences in smoking prevalence.

Regarding hypopharyngeal cancer, the incidence rates found in Spanish registries places Spain among countries with medium/ high rates within Europe, similarly to Switzerland, Slovakia,

and Slovenia. The highest age-standardized rates for both sexes within Europe were observed in France, particularly in regions characterized by traditionally high alcohol consumption.

The data presented herein demonstrates a reduction in the incidences of laryngeal and hypopharyngeal cancers in men, contrasting with an increase in rates for women in recent years in the populations of Girona and Tarragona. These reductions suggest the efficacy of current prevention strategies and highlight the importance of continuous application and even strengthening of these strategies. On the contrary, research has indicated variations in the rate of HPV-driven laryngeal cancer among countries, with some experiencing a slight increase in the number of HPV-positive laryngeal cancers. However, the importance of HPV in laryngeal cancer must be minor due to the parallel falling incidence of cancer and tobacco use.

9.6 NASOPHARYNGEAL CANCER

Among other subsites, we noted a stable or slightly decreasing trend in incidence of nasopharyngeal cancer. This trend is primarily influenced by a decrease in incidence among men, in contrast to a slightly increasing trend observed in women. This finding diverges from our initial hypothesis, as we anticipated an overall increase in nasopharyngeal cancer incidence in our region due to the migratory phenomenon from countries with a high prevalence of risk factors for nasopharyngeal cancer.

Nasopharyngeal cancer (NPC) is most prevalent in North Africa, Southeast Asia, and southern China, representing up to 18% of all malignancies among Asian populations. In Hong Kong, NPC ranks as the second most frequent tumor after lung cancer. Conversely, the incidence of this disease is relatively rare in Europe. The age-standardized incidence rate ($ASIR_W$) of NPC in China was 3.0 per 100,000 in 2018, approximately four times higher than the incidence rate in our studied population. This geographical disparity may stem from variations in exposure to risk factors for NPC across populations. Several types of exposure, such as wood dust, metal, industrial heat (e.g. furnaces, rolling mills, welding machines, etc.), motor fuel and oil, paints and varnishes, other chemicals (e.g. primarily acids, bases, solvents, detergents and soaps), and other types of smoke (e.g. from grass, oil, tars and other non-metallic sources) from construction sites, have been identified to have significant correlations with NPC and to have a higher prevalence in populations with higher risk for develop NPC (123).

The APC of NPC remained relatively unchanged, although there seems to be a discernible decrease, particularly in men. In our study, men are more frequently affected, with a male-to-female ratio of about 3:1. This observation aligns with the global distribution of NPC by sex, as indicated by the IARC. Males were more inclined to have occupations associated with NPC exposure compared to females, leading to increased occupational exposure to dust, physics, and chemical substances.

We have also observed that the majority of individuals in our study diagnosed with nasopharyngeal cancer fall within the age group of 0-49 years. NPC is robustly associated with EBV infection, often occurring during early childhood. Additionally, cultural, genetic, and environmental factors, including hepatitis B virus infection, have been implicated (124). The pronounced association of nasopharyngeal cancer with viral infections may explain why the affected population in this cancer subtype is predominantly younger compared to other subsites of head and neck cancer, which typically manifests at more advanced ages due to its correlation with exposure to risk factors such as tobacco and/or alcohol consumption. However, it is noteworthy that alcohol consumption and exposure to tobacco smoke at an early age have also been linked to a heightened risk of nasopharyngeal cancer.

Taking all of this into consideration, we can hypothesize that the reason for not observing an increasing trend in the incidence of nasopharyngeal cancer in our population is due to the fact that we have not yet experienced the migratory effect that is taking place globally in recent decades. Nevertheless, we anticipate that this trend in nasopharyngeal cancer incidence will change in the coming decades, reflecting an overall increase due to the rising migration from countries with a high incidence.

9.7 SINONASAL CANCER

Sinonasal cancer is also strongly associated with long-term occupational exposure to dust from hard wood or leather, with extremely high relative risks, as highlighted by the IARC. In our population, we identified a slightly non-significant decreasing trend in overall sinonasal cancer (APC -0.27) for both sexes. This aligns with the findings in European countries, North America, and the Asia-Pacific region, where the incidence of sinonasal cancer (all types) has remained relatively stable (125). We postulate that these trends are probably the result of less

occupational-related sinonasal cancer in recent years in our populations. In contrast, other studies in the United States report a slight increase in sinonasal cancer incidence, resembling epidemiological trends observed in other smoking-related tumours, such as lung cancer, linked to changes in smoking habits.

9.8 NOS PHARYNGEAL CANCER

With regard to NOS pharyngeal cancer, statistically non-significant changes were observed in either men or women during the study period, with an APC of -1.46. These results contradict our initial hypothesis, as we anticipated observing a decline in the overall incidence trend of NOS pharyngeal cancer due to improved diagnostic techniques in the later dates of the study calendar. Therefore, we cannot, based on our prior information, explain why the trend of NOS pharyngeal cancer has remained stable. Nevertheless, although not statistically significant, a discernible decreasing trend can be noted. Consequently, we estimate that this trend may become significant in the coming years. It is also worth noting that we cannot dismiss the possibility that the results are influenced by a small number of cases for this cancer subtype, which is acknowledged as a limitation of this study.

9.9 SALIVARY GLANDS CANCER

Concerning the outcomes of salivary gland cancer, it exhibits a statistically significant trend towards reduction, particularly among men. This aligns with findings from other Spanish registries. Incidence rates are higher in men; however, the sex difference is minimal, with a male-to-female ratio of 1.2:1. The low incidence and homogeneity of the rates present challenges in discussing the etiology of salivary gland cancers.

The unique established risk factor associated with major salivary gland cancer is exposure to ionizing radiation. High doses of radiation have been linked to the development of salivary gland cancer among survivors of the atomic bomb in the cancer registries of Hiroshima and Nagasaki (126). Consequently, we initially hypothesized that the incidence trend of salivary gland cancers would remain stable in our population. However, the study results do not align with this hypothesis.

Nevertheless, these significantly decreasing incidence results prompt us to consider that it may be attributed to improved histological classification of salivary gland tumors, particularly squamous cell carcinomas of the skin found in the parotid gland. Perhaps, by better classifying and, therefore, categorizing squamous cell carcinomas of the skin in the parotid as skin metastases rather than primary tumors of the parotid gland, a significant reduction in the number of salivary gland cancer cases in our region has occurred. This leads us to contemplate that this might not be a genuine decrease. However, other Spanish studies that have also observed this decrease in incidence find it challenging to identify the reasons contributing to the observed reduction in the Spanish population.

The substantial burden of HNC emphasizes the need for attention to the impact of this disease, considering it ranks as the seventh most common type of cancer worldwide. HNC is often preventable. Therefore, prevention strategies should be prioritized to help reduce the clinical burden of HNC by reducing or eliminating preventable risk factors, such as smoking and alcohol use. Cancer statistics serve as a vital component of evidence-based quality measure to inform decisions regarding public health interventions and resource planning. Additionally, they can also help to define the need for further research in particular areas.

This study provides a regional-specific approach of HNC incidence trends, which may afford knowledge for preventative measures and leveraging resources in order to reduce the burden of HNCs in our population. The decline in the incidence of tobacco related HNCs suggests the effectiveness of prevention measures targeting tobacco and alcohol consumption. However, the increase in the incidence of these cancers in women warrants attention, indicating a potential need for a revised strategy specific to women. Furthermore, the rising trend in oropharyngeal cancer incidence highlights the impact of HPV in our community, emphasizing the importance of implementing effective preventive measures such as HPV vaccination. Finally, the decrease in incidence of HNCs associated with occupational risk factors indicates positive progress in our efforts.

10. LIMITATIONS AND STRENGTHS

We acknowledge our sample size is not as large as in other population-based studies, as the provinces of Girona and Tarragona are regions with lower burden of some HNC subsites. This has impacted our results. For instance, in the lack of significance in trends for cancers of the oral cavity, oropharynx, pharynx (NOS) and sinonasal, in which observed APC rates tended to be statistically significant; their analysis would have had more statistical power with a higher number of cases and a longer time span.

Misclassification of cancer type by topography is another possible bias present in our study. It is inherent to the methodology of codification of tumours from the CRG and CRT and cannot be quantified. The anatomic proximity between the pharynx and other surrounding topographical sites, added to the similarity of risk factors, often results in erroneous classification of this type of cancer. Although the quality indicators of both registries are highly favourable, we cannot have complete certainty that all true HNC cases were well classified. Moreover, sometimes specifying the subsite becomes challenging, especially when the tumor exhibits considerable size and encompasses various anatomical subsites. This complexity may lead to misclassification in certain cases.

Having the CRG and the CRT as our database and the retrospective nature of our cohort, we were not able to collect further clinical information from study cases besides age and sex, which would have been useful for cofounder adjustment of our results. Plus, the lack of adjustment for cofounders regarding sex and age does not allow firm conclusions to be drawn regarding causal associations between key risk factors such as lifestyle, consumption of tobacco and alcohol, betel nut chewing, family history, and genetic characteristics, and these demographical features. It is relevant to consider that the provinces of Girona and Tarragona are regions of higher social economic status compared to other regions in Spain and Southern Europe, which could cause different distribution of behaviours on the mentioned risk factors associated to different HNC subsites.

The strengths of our study rely on the populational basis of our results, which can be extrapolated to the general populations of the provinces of Girona and Tarragona. We provide the first population-based report of all different HNC subsites in these populations. We also

give a wide time coverage of incidence trends, from 1994 until most recent time covered by the registries, 2018.

An additional strength of our study lies in the high reliability of data, evident in the high-quality data indicators of both employed population registers, with >95% completeness. Furthermore, the examination of incidence trends by subsites, adhering to the ICD-O-3 classification, enhances the credibility of our study. Lastly, to eliminate potential biases in comparing incidence rates with other populations, we opted to calculate Age-Standardized Incidence Rates (ASIR), both for European and World populations. This approach facilitates the comparison of our results with populations worldwide, using the European and global standard population models as benchmarks.

11. CONCLUSIONS

MAIN CONCLUSIONS

- There has been a significant **decrease** in the incidence of overall HNC from 1994 to 2018 in the provinces of Girona and Tarragona.
- There has been a **decrease** in the incidence of lip, hypopharyngeal, and laryngeal cancers between 1994 and 2018 in the provinces of Girona and Tarragona. Contrary to our hypothesis, the incidence of oral cavity, NOS pharynx, and sinonasal cancers has **remained unchanged**, indicating a non-significant decrease in the incidence over the same period.
- There has been a **decrease** in the incidence of salivary glands cancer between 1994 and 2018 in the provinces of Girona and Tarragona.
- There has been **no significant change** in the incidence of oropharyngeal cancer or nasopharyngeal cancer between 1994 and 2018 in the provinces of Girona and Tarragona. However, a non-significant increase in oropharyngeal cancer has been observed, while a non-significant decrease in incidence has been noted for nasopharyngeal cancer during the same period.
- Trends in the incidence of different HNC subsites have been observed to differ by sex between 1994 and 2018 in the provinces of Girona and Tarragona. Among men, a significant **decrease** in incidence has been noted in overall HNC, encompassing cancers of the lip, oral cavity, nasopharynx, hypopharynx, larynx, and salivary glands. In contrast, among women, a significant **increase** in the incidence of overall HNC has been observed, along with oral cavity, oropharyngeal, hypopharyngeal, and laryngeal cancers.

SECONDARY CONCLUSION

- Regarding to sex distribution of overall HNC and by subsite, all incidence rates were found to be higher for men than for women in the provinces of Girona and Tarragona between 1994 and 2018. Concerning age, patients between 40 and 85 years were found to have higher incidence rates of HNC. Mean age at diagnosis and age distribution significantly differ between men and women, with men presenting HNC at earlier ages than women. Significant differences were also found in age between sexes in cancers of the lip and oral cavity within the same period.

12. ETHICAL ASPECTS

The study had formal approval by the ethics committee of the *Hospital Universitari Josep Trueta de Girona (Comitè d'Ètica d'Investigació amb Medicaments de Girona (CEIM))* as reflected in *Annex 14*. Investigators strictly adhered to the provisions of the protocol submitted to the committee and to the standards of good clinical practice.

The study was performed in accordance with:

- The principles of the Declaration of Helsinki, adopted by the World Medical Association in Helsinki, in 1964, and last reviewed in 2013, ensuring alignment with human rights and ethical principles.
- The provision in the Ley Española 14/2007 del 3 de julio, on Biomedical Research.
- The standard of Good Clinical Practice issued by the Working Party on the Efficacy of Medicinal Products of the European Community in 1990 (CPMP/ICH/135/95) and the laws and regulations concerning these in force in Spain.
- The Oviedo Convention of April 4, 1997, on the protection of human rights and human dignity of the human being with regard to the application of biology and medicine, ratified in the Spanish Official Bulletin in October 1999.
- The provisions of the European Directive 1995/46/EC and the Ley Orgánica 3/2018 de 5 de diciembre regarding the guarantee of data protection, and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.
- The provisions of the European Directive 2001/83/EC and the Real Decreto 957/2020 on post-authorization observational studies.

Given that, the results of this study do not impact the diagnosis, treatment, or clinical monitoring of patients included in the study cohort. It is a retrospective study with anonymized data from the cancer registries of Girona and Tarragona; therefore, obtaining informed consent from patients is not required.

As it is an observational retrospective study without drug intervention, no adverse effects are expected, nor interference with prescribing habits of physicians or risk to subjects, and risk/benefit evaluation for patients is not deemed necessary. Given the nature of the study, in accordance with the Real Decreto 957/2020, no individual expedited notification of suspected adverse reactions is required.

Researchers had no conflict of interest. The primary motivation behind researchers' involvement was to generate knowledge about trends in incidence of head and neck cancer.

13. WORK PLAN AND CHRONOGRAM

The activities developed during the study happened in the following sequence, as in the timeline portrayed in *Table 9*.

STAGE 0: STUDY DESIGN

- **Activity 1:** bibliographic research about HNC and their subsites, HNC risk factors, their demographic characteristics, its impact in incidence, previous research on epidemiological trends of HNC cancer, and its clinical implication. The research has been performed in databases such as Clinical Trials and PubMed.
- **Activity 2**: protocol elaboration (objectives, hypotheses, variables, methods, ethical considerations, budget, planification).

STAGE 1: ETHICAL EVALUATION AND STUDY APPROVAL

- **Activity 3:** presentation of the protocol to the ethics committees of the Hospital Universitari Doctor Josep Trueta.
- **Activity 4:** correction of the protocol according to suggestions by the ethics committees and approval.

STAGE 2: CASE SELECTION

- **Activity 5**: review of the CRG and CRT database and selection of cases.
- **Activity 6:** Debugging of the database to allow us to calculate the incidence and the trends in incidence.

STAGE 3: DATA ANALYSIS AND INTERPRETATION

- **Activity 7:** statistical analyses, such as descriptive statistics, incidence, and trends in incidence of overall HNC and by subsite and differentiating by demographic characteristics such as sex and age.
- **Activity 8:** statistical interpretation of the results and elaboration of the manuscript (discussion and extraction of conclusions).

STAGE 4: PRESENTATION AND PUBLICATION OF FINDINGS

- **Activity 9:** presentation of results.
- **Activity 10:** publication of results as a journal article.

Table 8. Study chronogram

Stage	Task	2022	2023											2024	
		Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb
0	**A1**: bibliographic research															
	A2: protocol elaboration															
1	**A3**: presentation to CEIM															
	A4: CEIM approval															
2	**A5**: case selection															
	A6: data collection															
3	**A7**: statistical analyses															
	A8: statistical interpretation															
4	**A9**: presentation of results															
	A10: publication															

CEIM: ethics committee

14. BUDGET

There was no financial support for this study, all expenses were allocated from the GEDGPC funds. The extra budget apportioned for this project is solely designated for publication and dissemination expenses. This is attributed to the availability of the necessary data within the utilized database. The computers and programs employed for the execution of the present study are also part of routine usage of the GEDGPC. The research team is composed by the GEDGPC staff supposing no additional expense to the project. Material for the bibliography research has not represented an additional expense. No additional costs were sustained regarding tax application by the ethics committees or liability insurance.

Results will be published as a journal article. Considering the correction of language and the publication fees, the estimated subtotal of the publication costs is budgeted on 3.500€.

It is anticipated that the study will be presented at a national congress, as well as at the IACR Scientific Conference scheduled to take place in China in the fourth quarter of 2024. Taking into consideration the conference registration fees, travel expenses, and accommodation costs, the estimated subtotal for dissemination expenses is budgeted at 4000€.

The subsequent budget, described in *Table 9,* is an estimation of the expenses that this study may have incurred for GEDGPC.

Table 9. Summary of the study budget.

BUDGET		
ITEM	**COST**	**SUBTOTAL**
PERSONNEL EXPENSES (CRG and CRT technicians)		
Data collection	19.915€	22.165€
Data extraction and statistical analysis (45€/h, a total of 50h for this project)	2250€	
PUBLICATION EXPENSES		
Language proofreader	500€	3500€
Publication fee	3.000€	
DISSEMINATION EXPENSES		
National congress (inscription fee, travel and accommodation costs)	1500€	4500€
China international congress (inscription fee, travel and accommodation costs)	3000€	
		TOTAL: 30.165€

15. RESEARCH GROUP

The promoter of the study is the "*Grup d'Epidemiologia Descriptiva, Genètica I Prevenció del Càncer"* (GEDGPC) of "*Institut d'Investigació Biomèdica de Girona*" (IdIBGi), composed of epidemiologists, biologists, oncologists, and dermatologists from Girona. The research institute IdIBGi provides the necessary infrastructure for the management of the financial contributions of the projects and for their development (www.idibgi.org). This Institute was created in 2005 and is structured with research groups from the *Hospital Universitari Doctor Josep Trueta* in Girona, the University of Girona (UdG), the "*Institut de Diagnòstic per la Imatge*" (IDI), the "*Institut Català d'Oncologia*" (ICO), the "*Institut d'Assistència Sanitaria de Salt*" (IAS), and the "*Institut d'Atenció Primària*" (EAP) / "*Institut Català de Salut*" (ICS) in Girona. The members of the GEDGPC belong mostly to the ICO and to the ICS. The professionals of the Cancer Registry of Tarragona belong to the Pere Virgili Health Research Institute (IISPV) in Reus.

The members of the Group belong to different medical societies in their specialties and also take part in:

- RTICC RD12/0036/0056 *Red temática de Investigación en cáncer*. Strategic plan: tumours registry. *Epidemiológico, prevención y bioestadística* (Rafael Marcos-Gragera).
- EUROCARE Project, IARC (Rafael Marcos-Gragera).
- REDECAN. *Red de registros poblacionales de cáncer españoles* (Rafael Marcos-Gragera and Montserrat Puigdemont Guinart).
- GETTCC. *Grupo Español de Tratamiento de Tumores de Cabeza y Cuello* (Jordi Rubió).

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Montserrat Puigdemont Guinart:

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The Cancer Registry of Girona (CRG) and the Cancer Registry of Tarragona (CRT) are the two population-based cancer registries in Catalonia. They are members of the International Association of Cancer Registries (IACR), the European Network of Cancer Registries, and the Spanish Network of Cancer Registries (REDECAN). They are coordinated with the Oncology Master Plan of Catalonia, comply with all ethical and legal regulations for cancer case registration, and have the analytical capacity to conduct epidemiological studies.

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17. LIST OF TABLES AND FIGURES

18. ANNEXES

18.1 ANNEX 1: International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3)

HEAD AND NECK CANCER TOPOGRAPHICAL CODES (6)

C00-C14 LIP, ORAL CAVITY AND PHARYNX

C00 LIP *(excludes skin of lip C44.0)*

C00.0 External upper lip
Vermilion border of upper lip
Upper lip, NOS *(excludes skin of upper lip C44.0)*

C00.1 External lower lip
Vermilion border of lower lip
Lower lip, NOS *(excludes skin of lower lip C44.0)*

C00.2 External lip, NOS
Vermilion border of lip, NOS

C00.3 Mucosa of upper lip
Frenulum of upper lip
Inner aspect of upper lip

C00.4 Mucosa of lower lip
Inner aspect of lower lip
Frenulum of lower lip

C00.5 Mucosa of lip, NOS
Inner aspect of lip, NOS
Internal lip, NOS
Frenulum of lip, NOS
Frenulum labii, NOS

C00.6 Commissure of lip
Labial commissure

C00.8 Overlapping lesion of lip *(see section 4.2.6)*

C00.9 Lip, NOS *(excludes skin of lip C44.0)*

C01 BASE OF TONGUE

C01.9 Base of tongue, NOS
Dorsal surface of base of tongue
Posterior third of tongue
Posterior tongue, NOS
Root of tongue

C02 OTHER AND UNSPECIFIED PARTS OF TONGUE

C02.0 Dorsal surface of tongue, NOS
Anterior 2/3 of tongue, dorsal surface
Midline of tongue
Dorsal surface of anterior tongue

C02.1 Border of tongue
Tip of tongue

C02.2 Ventral surface of tongue, NOS
Anterior 2/3 of tongue, ventral surface
Frenulum linguae
Ventral surface of anterior tongue, NOS

C02.3 Anterior 2/3 of tongue, NOS
Anterior tongue, NOS

C02.4 Lingual tonsil

C02.8 Overlapping lesion of tongue
(see section 4.2.6)
Junctional zone of tongue

C02.9 Tongue, NOS
Lingual, NOS

C03 GUM

C03.0 Upper gum
Maxillary gingiva
Upper alveolar mucosa
Upper alveolar ridge mucosa
Upper alveolus
Upper gingiva

C03.1 Lower gum
Mandibular gingiva
Lower alveolar mucosa
Lower alveolar ridge mucosa
Lower alveolus
Lower gingiva

C03.9 Gum, NOS
Gingiva, NOS
Alveolar mucosa, NOS
Alveolar ridge mucosa, NOS
Alveolus, NOS
Periodontal tissue
Tooth socket

C04 FLOOR OF MOUTH

C04.0 Anterior floor of mouth

C04.1 Lateral floor of mouth

C04.8 Overlapping lesion of floor of mouth *(see section 4.2.6)*

C04.9 Floor of mouth, NOS

C05 PALATE

C05.0 Hard palate

C05.1 Soft palate, NOS *(excludes nasopharyngeal surface of soft palate C11.3)*

C05.2 Uvula

C05.8 Overlapping lesion of palate *(see section 4.2.6)*
Junction of hard and soft palate

C05.9 Palate, NOS
Roof of mouth

C06 OTHER AND UNSPECIFIED PARTS OF MOUTH

C06.0 Cheek mucosa
Buccal mucosa
Internal cheek

C06.1 Vestibule of mouth
Alveolar sulcus
Buccal sulcus
Labial sulcus

C06.2 Retromolar area
Retromolar triangle
Retromolar trigone

C06.8 Overlapping lesion of other and unspecified parts of mouth *(see section 4.2.6)*

C06.9 Mouth, NOS
Buccal cavity
Oral cavity
Oral mucosa
Minor salivary gland, NOS *(see section 4.3.5)*

C07 PAROTID GLAND

C07.9 Parotid gland
Parotid, NOS
Stensen duct
Parotid gland duct

C08 OTHER AND UNSPECIFIED MAJOR SALIVARY GLANDS

Note: *Neoplasms of minor salivary glands should be classified according to their anatomical site; if location is not specified, classify to C06.9*

C08.0 Submandibular gland
Submaxillary gland
Wharton duct
Submaxillary gland duct

C08.1 Sublingual gland
Sublingual gland duct

C08.8 Overlapping lesion of major salivary glands *(see section 4.2.6)*

C08.9 Major salivary gland, NOS
Salivary gland, NOS *(see section 4.3.5) (excludes minor salivary gland, NOS C06.9)*

C09 TONSIL

C09.0 Tonsillar fossa

C09.1 Tonsillar pillar
Faucial pillar
Glossopalatine fold

C09.8 Overlapping lesion of tonsil *(see section 4.2.6)*

C09.9 Tonsil, NOS *(excludes lingual tonsil C02.4 and pharyngeal tonsil C11.1)*
Faucial tonsil
Palatine tonsil

C10 OROPHARYNX

C10.0 Vallecula

C10.1 Anterior surface of epiglottis

C10.2 Lateral wall of oropharynx
Lateral wall of mesopharynx

C10.3 Posterior wall of oropharynx
Posterior wall of mesopharynx

C10.4 Branchial cleft *(site of neoplasm)*

C10.8 Overlapping lesion of oropharynx *(see section 4.2.6)*
Junctional region of oropharynx

C10.9 Oropharynx, NOS
Mesopharynx, NOS
Fauces, NOS

C11 NASOPHARYNX

C11.0 Superior wall of nasopharynx
Roof of nasopharynx

C11.1 Posterior wall of nasopharynx
Adenoid
Pharyngeal tonsil

C11.2 Lateral wall of nasopharynx
Fossa of Rosenmuller

C11.3 Anterior wall of nasopharynx
Nasopharyngeal surface of soft palate
Pharyngeal fornix
Choana
Posterior margin of nasal septum

C11.8 Overlapping lesion of nasopharynx *(see section 4.2.6)*

C11.9 Nasopharynx, NOS
Nasopharyngeal wall

C12 PYRIFORM SINUS

C12.9 Pyriform sinus
Piriform sinus
Pyriform fossa
Piriform fossa

C13 HYPOPHARYNX

C13.0 Postcricoid region
Cricopharynx
Cricoid, NOS

C13.1 Hypopharyngeal aspect of aryepiglottic fold
Aryepiglottic fold, NOS *(excludes laryngeal aspect of aryepiglottic fold C32.1)*
Arytenoid fold

C13.2 Posterior wall of hypopharynx

C13.8 Overlapping lesion of hypopharynx *(see section 4.2.6)*

C13.9 Hypopharynx, NOS
Hypopharyngeal wall
Laryngopharynx

C14 OTHER AND ILL-DEFINED SITES IN LIP, ORAL CAVITY AND PHARYNX

C14.0 Pharynx, NOS
Pharyngeal wall, NOS
Wall of pharynx, NOS
Lateral wall of pharynx, NOS
Posterior wall of pharynx, NOS
Retropharynx
Throat

C14.2 Waldeyer ring

C14.8 Overlapping lesion of lip, oral cavity and pharynx *(see section 4.2.6)*
Note: *Neoplasms of lip, oral cavity and pharynx whose point of origin cannot be assigned to any one of the categories C00 to C14.2*

C30-C39 RESPIRATORY SYSTEM AND INTRATORACIC ORGANS

C30 NASAL CAVITY AND MIDDLE EAR

C30.0 Nasal cavity *(excludes nose, NOS C76.0)*
Internal nose
Naris
Nasal cartilage
Nasal mucosa
Nasal septum, NOS *(excludes posterior margin of nasal septum C11.3)*
Nasal turbinate
Nostril
Vestibule of nose

C31 ACCESSORY SINUSES

C31.0 Maxillary sinus
Maxillary antrum
Antrum, NOS

C31.1 Ethmoid sinus

C31.2 Frontal sinus

C31.3 Sphenoid sinus

C31.8 Overlapping lesion of accessory sinuses *(see section 4.2.6)*

C31.9 Accessory sinus, NOS
Accessory nasal sinus
Paranasal sinus

C32 LARYNX

C32.0 Glottis
Intrinsic larynx
Laryngeal commissure
Vocal cord, NOS
True vocal cord
True cord

C32.1 Supraglottis
Epiglottis, NOS *(excludes anterior surface of epiglottis C10.1)*
Extrinsic larynx
Laryngeal aspect of aryepiglottic fold
Posterior surface of epiglottis
Ventricular band of larynx
False vocal cord
False cord

C32.2 Subglottis

C32.3 Laryngeal cartilage
Arytenoid cartilage
Cricoid cartilage
Cuneiform cartilage
Thyroid cartilage

C32.8 Overlapping lesion of larynx *(see section 4.2.6)*

C32.9 Larynx, NOS

18.2 ANNEX 2: Incidence rates calculation

$$cruderate = \frac{count}{population} \times 100,000$$

$$\text{ASR} = \left(\frac{\text{Number of new cases in an age group}}{\text{Population in that age group}}\right) \times \text{Factor (usually 100,000)}$$

$$\text{ASIR} = \sum_{\text{all age groups}} (\text{ASR} \times \text{Weight from European Standard Population})$$

$$\text{ASIR} = \sum_{\text{all age groups}} (\text{ASR} \times \text{Weight from World Standard Population})$$

Table 10. 2013 European standard population. Extracted from (127).

Age Group (years)	Standard Population
0,0	1 000
1-4	4 000
5-9	5 500
10-14	5 500
15-19	5 500
20-24	6 000
25-29	6 000
30-34	6 500
35-39	7 000
40-44	7 000
45-49	7 000
50-54	7 000
55-59	6 500
60-64	6 000
65-69	5 500
70-74	5 000
75-79	4 000
80-84	2 500
85-89	1 500
90-94	800
95+	200
Total	**100 000**

Table 11. Segi's world standard population. Extracted from (128).

Age group (yr)	No. of population
0-4	12,000
5-9	10,000
10-14	9,000
15-19	9,000
20-24	8,000
25-29	8,000
30-34	6,000
35-39	6,000
40-44	6,000
45-49	6,000
50-54	5,000
55-59	4,000
60-64	4,000
65-69	3,000
70-74	2,000
75-79	1,000
80-84	500
≥ 85	500
Total	100,000

18.3 ANNEX 3: Morphologies of overall head and neck cancer

Table 12. Number of cases and percentage of tumor morphologies of overall head and neck cancer in Girona and Tarragona 1994-2018.

Morphology	N	%
8000/3 - Malignant neoplasm	320	4.02
8003/3 - Malignant tumor of giant cells	1	0.01
8010/3 - Carcinoma, NOS	131	1.64
8012/3 - Carcinoma of large cells, NOS	17	0.21
8013/3 - Neuroendocrine carcinoma of large cells	2	0.03
8020/3 - Undifferentiated carcinoma, NOS	68	0.85
8021/3 - Anaplastic carcinoma, NOS	1	0.01
8022/3 - Pleomorphic carcinoma	2	0.03
8033/3 - Pseudosarcomatous carcinoma	12	0.15
8034/3 - Carcinoma of polygonal cells	1	0.01
8041/3 - Carcinoma of small cells, NOS	13	0.16
8046/3 - Carcinoma of non-small cells (c34.-)	1	0.01
8051/3 - Verrucous carcinoma, NOS	85	1.07
8052/3 - Papillary squamous cell carcinoma	11	0.14
8070/3 - Squamous cell carcinoma, NOS	5,96	74.82
8071/3 - Squamous cell carcinoma, keratinizing type, NOS	654	8.21
8072/3 - Squamous cell carcinoma, large non-keratinizing type, NOS	176	2.21
8073/3 - Squamous cell carcinoma, small non-keratinizing type	4	0.05
8074/3 - Squamous cell carcinoma, spindle cell type	15	0.19
8075/3 - Squamous cell carcinoma, adenoide type	3	0.04
8076/3 - Squamous cell carcinoma, microinvasive	19	0.24
8082/3 - Lymphoepithelial carcinoma	82	1.03
8083/3 - Basaloid carcinoma of squamous cells	31	0.39
8084/3 - Squamous cell carcinoma, clear cell type	5	0.06
8085/3 - Scatous carcinoma, HPV-positive	3	0.04
8086/3 - Scatous carcinoma, HPV-negative	1	0.01
8120/3 - Transitional cell carcinoma, NOS	3	0.04
8121/3 - Schneider carcinoma, (c30.0, c31._)	1	0.01
8123/3 - Basaloid carcinoma	3	0.04
8130/3 - Papillary transitional cell carcinoma (c67._)	1	0.01

8140/3 - Adenocarcinoma, NOS	65	0.82
8144/3 - Adenocarcinoma, intestinal type (c16._)	7	0.09
8147/3 - Basaloid adenocarcinoma.	6	0.08
8200/3 - Cystadenocarcinoma	71	0.89
8240/3 - Neuroendocrine tumor, NOS	2	0.03
8246/3 - Neuroendocrine carcinoma, NOS	5	0.06
8249/3 - Neuroendocrine tumor, grade 2	1	0.01
8290/3 - Oxyphilic adenocarcinoma	1	0.01
8310/3 - Clear cell adenocarcinoma, NOS	2	0.03
8410/3 - Sebaceous carcinoma (c44._)	1	0.01
8430/3 - Mucoepidermoid carcinoma	88	1.10
8440/3 - Cystoadenocarcinoma, NOS	2	0.03
8480/3 - Mucinous adenocarcinoma	3	0.04
8481/3 - Mucin-secreting adenocarcinoma	4	0.05
8500/3 - Infiltrating ductal carcinoma (c50._)	16	0.20
8525/3 - Polymorphous adenocarcinoma	2	0.03
8550/3 - Acinar cell carcinoma	40	0.50
8560/3 - Adenosquamous carcinoma	13	0.16
8562/3 - Epithelial-myoepithelial carcinoma	10	0.13
8711/3 - Malignant glomus tumor	1	0.01
Total	7,966	100.00

18.4 ANNEX 4: Morphologies of lip cancer

Table 13. Number of cases and percentage of tumor morphologies of lip cancer in Girona and Tarragona 1994-2018.

Morphology	N	%
8010/3 - Carcinoma, NOS	3	0.31
8051/3 - Warty carcinoma, NOS	10	1.03
8070/3 - Squamous cell carcinoma, NOS	822	84.57
8071/3 - Squamous cell carcinoma, keratinizing type, NOS	111	11.42
8072/3 - Squamous cell carcinoma, large cell, non-keratinizing type, NOS	1	0.10
8074/3 - Squamous cell carcinoma, spindle cell type	2	0.21
8075/3 - Squamous cell carcinoma, adenoacanthoma	1	0.10
8076/3 - Squamous cell carcinoma, microinvasive	8	0.82
8410/3 - Sebaceous carcinoma (c44._)	1	0.10
8430/3 - Mucoepidermoid carcinoma	3	0.31
Total	972	100.00

18.5 ANNEX 5: Morphologies of oral cavity cancer

Table 14. Number of cases and percentage of tumor morphologies of oral cavity cancer in Girona and Tarragona 1994-2018.

Morphology	N	%
8010/3 - Carcinoma, NOS	18	1.06
8012/3 - Large cell carcinoma, NOS	1	0.06
8020/3 - Undifferentiated carcinoma, NOS	2	0.12
8022/3 - Pleomorphic carcinoma	1	0.06
8033/3 - Pseudosarcomatous carcinoma	2	0.12
8041/3 - Small cell carcinoma, NOS	1	0.06
8051/3 - Warty carcinoma, NOS	44	2.59
8052/3 - Papillary squamous cell carcinoma	3	0.18
8070/3 - Squamous cell carcinoma, NOS	1,324	77.84
8071/3 - Squamous cell carcinoma, keratinizing type, NOS	168	9.88
8072/3 - Squamous cell carcinoma, large cell, non-keratinizing type, NOS	25	1.47
8073/3 - Squamous cell carcinoma, small cell, non-keratinizing type	1	0.06
8074/3 - Squamous cell carcinoma, spindle cell type	3	0.18
8075/3 - Squamous cell carcinoma, adenoacanthoma	1	0.06
8076/3 - Squamous cell carcinoma, microinvasive	4	0.24
8082/3 - Lymphoepithelial carcinoma	1	0.06
8083/3 - Basaloid squamous cell carcinoma	5	0.29
8140/3 - Adenocarcinoma, NOS	9	0.53
8200/3 - Cystadenocarcinoma	16	0.94
8310/3 - Clear cell adenocarcinoma, NOS	1	0.06
8430/3 - Mucoepidermoid carcinoma	21	1.23
8440/3 - Cystadenocarcinoma, NOS	1	0.06
8480/3 - Mucinous adenocarcinoma	1	0.06
8525/3 - Polymorphous adenocarcinoma	1	0.06
8550/3 - Acinar cell carcinoma	1	0.06
8560/3 - Adenosquamous carcinoma	3	0.18
8562/3 - Epithelial-myoepithelial carcinoma	1	0.06
Total	1,701	100.00

18.6 ANNEX 6: Morphologies of oropharyngeal cancer

Table 15. Number of cases and percentage of tumor morphologies of oropharyngeal cancer in Girona and Tarragona 1994-2018.

Morphology	N	%
8000/3 - Malignant neoplasm	36	3.15
8010/3 - Carcinoma, NOS	16	1.40
8012/3 - Large cell carcinoma, NOS	3	0.26
8013/3 - Large cell neuroendocrine carcinoma	1	0.09
8020/3 - Undifferentiated carcinoma, NOS	3	0.26
8041/3 - Small cell carcinoma, NOS	1	0.09
8051/3 - Warty carcinoma, NOS	4	0.35
8052/3 - Papillary squamous cell carcinoma	3	0.26
8070/3 - Squamous cell carcinoma, NOS	930	81.29
8071/3 - Squamous cell carcinoma, keratinizing type, NOS	62	5.42
8072/3 - Squamous cell carcinoma, large cell, non-keratinizing type, NOS	45	3.93
8074/3 - Squamous cell carcinoma, spindle cell type	1	0.09
8082/3 - Lymphoepithelial carcinoma	4	0.35
8083/3 - Basaloid squamous cell carcinoma	5	0.44
8084/3 - Squamous cell carcinoma, clear cell type	1	0.09
8085/3 - Squamous cell carcinoma, HPV-positive, scatologic type	3	0.26
8123/3 - Basaloid carcinoma	1	0.09
8140/3 - Adenocarcinoma, NOS	5	0.44
8200/3 - Cystadenocarcinoma	10	0.87
8430/3 - Mucoepidermoid carcinoma	9	0.79
8560/3 - Adenosquamous carcinoma	1	0.09
Total	1,144	100.00

18.7 ANNEX 7: Morphologies of nasopharyngeal cancer

Table 16. Number of cases and percentage of tumor morphologies of nasopharyngeal cancer in Girona and Tarragona 1994-2018.

Morphology	N	%
8010/3 - Carcinoma, NOS	25	9.36
8012/3 - Large cell carcinoma, NOS	3	1.12
8020/3 - Undifferentiated carcinoma, NOS	40	14.98
8034/3 - Polygonal cell carcinoma	1	0.37
8070/3 - Squamous cell carcinoma, NOS	72	26.97
8071/3 - Squamous cell carcinoma, keratinizing type, NOS	6	2.25
8072/3 - Squamous cell carcinoma, large cell, non-keratinizing type, NOS	34	12.73
8073/3 - Squamous cell carcinoma, small cell, non-keratinizing type	2	0.75
8082/3 - Lymphoepithelial carcinoma	67	25.09
8120/3 - Transitional cell carcinoma, NOS	1	0.37
8140/3 - Adenocarcinoma, NOS	1	0.37
8200/3 - Cystadenocarcinoma	1	0.37
8430/3 - Mucoepidermoid carcinoma	1	0.37
8560/3 - Adenosquamous carcinoma	1	0.37
8562/3 - Epithelial-myoepithelial carcinoma	1	0.37
Total	267	100.00

18.8 ANNEX 8: Morphologies of hypopharyngeal cancer

Table 17. Number of cases and percentage of tumor morphologies of hypopharyngeal cancer in Girona and Tarragona 1994-2018.

Morphology	N	%
8010/3 - Carcinoma, NOS	12	1.93
8012/3 - Large cell carcinoma, NOS	1	0.16
8020/3 - Undifferentiated carcinoma, NOS	4	0.64
8033/3 - Pseudosarcomatous carcinoma	2	0.32
8041/3 - Small cell carcinoma, NOS	2	0.32
8051/3 - Warty carcinoma, NOS	1	0.16
8070/3 - Squamous cell carcinoma, NOS	489	78.49
8071/3 - Squamous cell carcinoma, keratinizing type, NOS	55	8.83
8072/3 - Squamous cell carcinoma, large cell, non-keratinizing type, NOS	18	2.89
8074/3 - Squamous cell carcinoma, spindle cell type	3	0.48
8082/3 - Lymphoepithelial carcinoma	3	0.48
8083/3 - Basaloid squamous cell carcinoma	4	0.64
8084/3 - Squamous cell carcinoma, clear cell type	2	0.32
8123/3 - Basaloid carcinoma	1	0.16
8140/3 - Adenocarcinoma, NOS	1	0.16
8246/3 - Neuroendocrine carcinoma, NOS	2	0.32
Total	623	100.00

18.9 ANNEX 9: Morphologies of pharyngeal cancer (NOS)

Table 18. Number of cases and percentage of tumor morphologies of pharyngeal cancer (NOS) in Girona and Tarragona 1994-2018.

Morphology	N	%
8010/3 - Carcinoma, NOS	3	4.76
8033/3 - Pseudosarcomatous carcinoma	1	1.59
8070/3 - Squamous cell carcinoma, NOS	42	66.67
8071/3 - Squamous cell carcinoma, keratinizing type, NOS	5	7.94
8072/3 - Squamous cell carcinoma, large cell, non-keratinizing type, NOS	3	4.76
8075/3 - Squamous cell carcinoma, adenoide type	1	1.59
8083/3 - Basaloid squamous cell carcinoma	1	1.59
8140/3 - Adenocarcinoma, NOS	1	1.59
8481/3 - Mucin-secreting adenocarcinoma	1	1.59
Total	63	100.00

18.10 ANNEX 10: Morphologies of laryngeal cancer

Table 19. Number of cases and percentage of tumor morphologies of laryngeal cancer in Girona and Tarragona 1994-2018.

Morphology	N	%
8010/3 - Carcinoma, NOS	21	0.79
8012/3 - Large cell carcinoma, NOS	1	0.04
8013/3 - Large cell neuroendocrine carcinoma	1	0.04
8020/3 - Undifferentiated carcinoma, NOS	4	0.15
8033/3 - Pseudosarcomatous carcinoma	6	0.23
8041/3 - Small cell carcinoma, NOS	2	0.08
8051/3 - Warty carcinoma, NOS	26	0.98
8052/3 - Papillary squamous cell carcinoma	3	0.11
8070/3 - Squamous cell carcinoma, NOS	2,128	80.27
8071/3 - Squamous cell carcinoma, keratinizing type, NOS	222	8.37
8072/3 - Squamous cell carcinoma, large cell, non-keratinizing type, NOS	45	1.70
8074/3 - Squamous cell carcinoma, spindle cell type	5	0.19
8076/3 - Microinvasive squamous cell carcinoma	7	0.26
8083/3 - Basaloid squamous cell carcinoma	14	0.53
8086/3 - Scatological carcinoma, HPV-negative	1	0.04
8140/3 - Adenocarcinoma, NOS	2	0.08
8240/3 - Neuroendocrine tumor, NOS	1	0.04
8246/3 - Neuroendocrine carcinoma, NOS	2	0.08
8430/3 - Mucoepidermoid carcinoma	2	0.08
8560/3 - Adenosquamous carcinoma	7	0.26
Total	2,651	100.00

18.11 ANNEX 11: Morphologies of sinonasal cancer

Table 20. Number of cases and percentage of tumor morphologies of sinonasal cancer in Girona and Tarragona 1994-2018.

Morphology	N	%
8010/3 - Carcinoma, NOS	3	1.42
8012/3 - Large cell carcinoma, NOS	1	0.47
8020/3 - Undifferentiated carcinoma, NOS	8	3.79
8021/3 - Anaplastic carcinoma, NOS	1	0.47
8033/3 - Pseudosarcomatous carcinoma	1	0.47
8041/3 - Small cell carcinoma, NOS	3	1.42
8052/3 - Papillary squamous cell carcinoma	2	0.95
8070/3 - Squamous cell carcinoma, NOS	96	45.50
8071/3 - Squamous cell carcinoma, keratinizing type, NOS	13	6.16
8072/3 - Squamous cell carcinoma, large cell, non-keratinizing type, NOS	3	1.42
8073/3 - Squamous cell carcinoma, small cell, non-keratinizing type	1	0.47
8074/3 - Squamous cell carcinoma, spindle cell type	1	0.47
8082/3 - Lymphoepithelial carcinoma	1	0.47
8083/3 - Basaloid squamous cell carcinoma	1	0.47
8120/3 - Transitional cell carcinoma, NOS	2	0.95
8121/3 - Schneiderian carcinoma, NOS	1	0.47
8130/3 - Papillary transitional cell carcinoma	1	0.47
8140/3 - Adenocarcinoma, NOS	24	11.37
8144/3 - Adenocarcinoma, intestinal type	7	3.32
8147/3 - Basaloid adenocarcinoma	1	0.47
8200/3 - Adenoid cystic carcinoma	12	5.69
8240/3 - Neuroendocrine tumor, NOS	1	0.47
8246/3 - Neuroendocrine carcinoma, NOS	1	0.47
8249/3 - Neuroendocrine tumor, grade 2	1	0.47
8310/3 - Clear cell adenocarcinoma, NOS	1	0.47
8480/3 - Mucinous adenocarcinoma	2	0.95
8481/3 - Mucin-secreting adenocarcinoma	3	1.42
8550/3 - Acinar cell carcinoma	1	0.47
8562/3 - Epithelial-myoepithelial carcinoma	2	0.95
8711/3 - Malignant glomus tumor	1	0.47
Total	211	100.00

18.12 ANNEX 12: Morphologies of salivary glands cancer

Table 21. Number of cases and percentage of tumor morphologies of salivary glands cancer in Girona and Tarragona 1994-2018.

Morphology	N	%
8003/3 - Giant cell malignant tumor	1	0.30
8010/3 - Carcinoma, NOS	30	8.98
8012/3 - Large cell carcinoma, NOS	7	2.10
8020/3 - Undifferentiated carcinoma, NOS	7	2.10
8022/3 - Pleomorphic carcinoma	1	0.30
8041/3 - Small cell carcinoma, NOS	4	1.20
8046/3 - Non-small cell carcinoma (c34.-)	1	0.30
8070/3 - Squamous cell carcinoma, NOS	57	17.07
8071/3 - Squamous cell carcinoma, keratinizing type, NOS	12	3.59
8072/3 - Squamous cell carcinoma, large cell, non-keratinizing type, NOS	2	0.60
8082/3 - Lymphoepithelial carcinoma	6	1.80
8083/3 - Basaloid squamous cell carcinoma	1	0.30
8084/3 - Squamous cell carcinoma, clear cell type	2	0.60
8123/3 - Basaloid carcinoma	1	0.30
8140/3 - Adenocarcinoma, NOS	22	6.59
8147/3 - Basal cell adenocarcinoma	5	1.50
8200/3 - Cystadenocarcinoma	32	9.58
8290/3 - Oxyphilic adenocarcinoma	1	0.30
8430/3 - Mucoepidermoid carcinoma	52	15.57
8440/3 - Cystadenocarcinoma, NOS	1	0.30
8500/3 - Infiltrating ductal carcinoma (c50._)	16	4.79
8525/3 - Polymorphous adenocarcinoma	1	0.30
8550/3 - Acinar cell carcinoma	38	11.38
8560/3 - Adenosquamous carcinoma	1	0.30
8562/3 - Epithelial-myoepithelial carcinoma	6	1.80
Total	334	100.00

18.13 ANNEX 13: Age-specific rates for head and neck cancer

Table 22. Age-specific rates (ASR) of overall head and neck cancer stratified by five-year groups, Girona and Tarragona (1994-2018).

Grups d'edat	N	Persones-any	TEE	LowerCI	UpperCI
0-4	0	1,788,118	0.00	0.00	0.21
5-9	0	1,768,179	0.00	0.00	0.21
10-14	2	1,744,902	0.11	0.01	0.41
15-19	8	1,864,126	0.43	0.19	0.85
20-24	16	2,151,177	0.74	0.42	1.21
25-29	17	2,483,131	0.68	0.40	1.10
30-34	46	2,732,981	1.68	1.23	2.25
35-39	123	2,806,345	4.38	3.64	5.23
40-44	309	2,659,411	11.62	10.36	12.99
45-49	550	2,429,564	22.64	20.79	24.61
50-54	867	2,181,465	39.74	37.14	42.48
55-59	1,019	1,915,138	53.21	49.99	56.58
60-64	1,139	1,737,018	65.57	61.82	69.49
65-69	1,069	1,588,961	67.28	63.30	71.43
70-74	946	1,395,693	67.78	63.53	72.24
75-79	834	1,147,373	72.69	67.84	77.79
80-84	582	860,816	67.61	62.23	73.33
85+	439	1,323,283	33.18	30.14	36.43

N: absolute number of cases; TEE: Age-Standardized Rate (ASR) by its initials in Spanish *"Tasa Especifica por Edad".*

18.14 ANNEX 14: Approval of the Research Ethics Committee

Salut/ Trueta Hospital de Girona

IAS Institut d'Assistència Sanitària

INFORME DEL COMITÈ D'ÈTICA D'INVESTIGACIÓ AMB MEDICAMENTS CEIM GIRONA

El Comitè d'Ètica d'Investigació amb Medicaments CEIM GIRONA en la reunió del 27/03/2023 (Acta 4/2023) després de l'avaluació de l'estudi:

Títol: Anàlisis en base poblacional de la tendència de la incidència dels càncers de cap i coll a Girona i Tarragona en el període 1994-2018
Codi Protocol: GEDGPC-CC-2023-01
Documents amb versions:
Protocol v1.0:01/02/2023
Investigador principal: JORDI RUBIÓ CASADEVALL
Promotor: IDIBGI - INSTITUT D'INVESTIGACIÓ BIOMÈDICA DE GIRONA DR. JOSEP TRUETA - Grup d'Epidemiologia Descriptiva, Genètica i Prevenció del Càncer
Codi. CEIM: 2023.062

considera que:

1. L'estudi avaluat compleix els requisits metodològics i tècnics.
2. La competència dels investigadors i els mitjans disponibles són apropiats per dur a terme l'estudi.
3. Els riscos i molèsties previsibles de la investigació són acceptables en relació amb els beneficis esperats.
4. El procés de selecció dels participants és apropiat.
5. S'accepta l'exempció de consentiment proposat per aquest estudi.
6. Les compensacions econòmiques previstes són adequades i no interfereixen amb la resta de postulats ètics.
7. El CEIM GIRONA , tant en la seva composició como en els seus PNT's, compleix amb les normes de BPC (CPMP/ICH/135/95).

I EMET INFORME FAVORABLE per la realització de l'estudi

Sra. Marta Riera Juncà
Secretària Tècnica CEIM Girona
Girona, 03 maig 2023

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Generalitat de Catalunya
Departament de Salut