Incidence, trends in incidence and survival analysis in Head and Neck Cancer from 1994 to 2013 in Girona, Spain:

A population-based study

Universitat de Girona

FINAL DEGREE PROJECT

Unitat d'Epidemiologia i Registre de Càncer de Girona (UERCG)

Author: Òscar Moreno Felici

Tutor: Dr. Jordi Rubió Casadevall

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ABBREVIATIONS

Abbreviation	Meaning
AAA	Adenomas and adenocarcinomas
ACN	Acinar cell neoplasms
APC	Annual percentage change
ASR_E	Age-standardized to the European standard population
ASR_W	Age-standardized to the World standard population
CI	Confidence interval
CR	Crude rate
DCO	Death certificate only
EBV	Epstein-Barr virus
ENCR	European Network for Cancer Registries
FDP	Final Degree Project
GCR	Girona Cancer Registry
HNC	Head and Neck Cancer
HPV	Human papilloma virus
IACR	International Association of Cancer Registries
ICD-O-3	International Classification of Diseases for Oncology, 3th edition
IDESCAT	*Institut d'Estadística de Catalunya*
MN	Mucoepidermoid neoplasms
MV	Microscopic verification
NE	Not specified
NOS	Not otherwise specified
SCN	Squamous cell neoplasms
SD	Standard deviation
UC	Undifferentiated carcinoma
USA	United States of America
WHO	World Health Organization's

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ABSTRACT

Introduction: Head and Neck Cancer (HNC) is a highly heterogeneous disease comprising a large number of tumours located in the cervicofacial area. This study aimed to determine the epidemiological characteristics of HNC and its topographic sites.

Data/Methods: 3171 patients with a HNC (470 lips, 767 oral cavity, 147 salivary glands, 294 oropharyngeal, 124 nasopharyngeal, 240 hypopharyngeal, 45 not specified (NE) pharyngeal, 112 nose, ear and sinuses and 972 laryngeal cancers) registered in Girona Cancer Registry (GCR) in Spain during the period of 1994-2013 were analysed to estimate their incidence, trends in incidence and observed survival.

Results: Most patients were males (82.9%) between 50 and 74 years (64%). Relative to histological subtype, squamous cell neoplasms (SCN) was the most frequent in both sexes. Oral cavity was the most common topographic site in women, being the larynx for men and both sexes. Incidence decreased significantly in HNC for men and both sexes with annual percentage of change (APC) of -2.5 and -2.0, respectively, but not in oropharyngeal cancer. Five-year HNC observed survival for both sexes was 50.2%.

Conclusions: Our study confirms the higher HNC incidence in men compared to women, being the most frequent topographic site the larynx and the oral cavity respectively. Also the decreasing incidence of HNC is confirmed with the exception of oropharyngeal cancer that its incidence remained the same during the study period. In terms of survival, good results were found. SCN are confirmed as the most common histological type regardless of sex or age.

Keywords: head and neck cancer; squamous cell neoplasms; undifferentiated carcinoma; adenomas and adenocarcinomas; mucoepidermoid neoplasms; acinar cell neoplasms; incidence; survival; population-based cancer registry; epidemiology; HPV.

CONTENTS

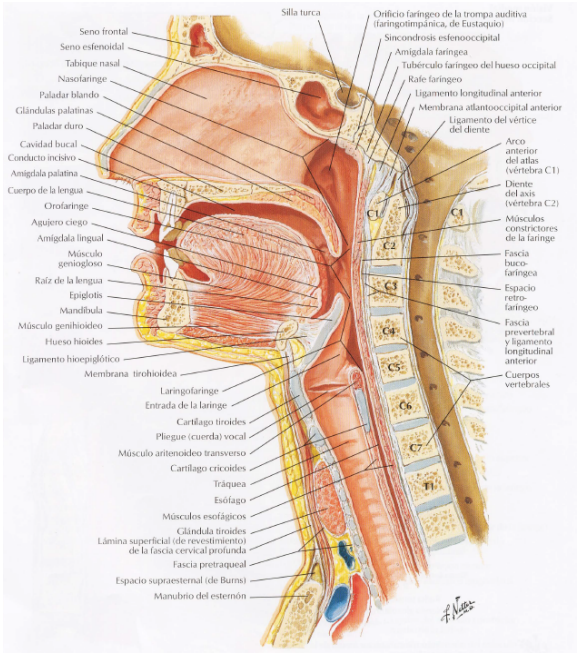
INTRODUCTION

Head and Neck Cancer: Classification of topographic sites

Head and Neck Cancers (HNC) can occur in any of the tissues or organ in the head and neck. For that reason, over 30 different places can develop cancer in the cervicofacial area. These places can be grouped into 9 large topographic sites: lips, oral cavity, salivary glands, oropharynx, nasopharynx, hypopharynx, NE pharynx, nose, ear and sinuses and larynx. Within this classification, tumours of the skin, brain and thyroid are excluded(1).

- Most **lip** cancers occur on the bottom lip.
- **Oral cavity** is the most common place for head and neck cancer to develop(2). Includes the front two-thirds of the tongue, the gums, the lining inside the cheeks and lips, the floor (bottom) of the mouth under the tongue, the hard palate (bony top of the mouth), and the small area of the gum behind the wisdom teeth (see **Annex 1**). The most frequent affected places are the side of the tongue and the floor of the mouth.

Figure 1. Picture showing a cross-section of the head(3).



- The **nasopharynx** is the upper part of the throat behind the nose.
- The **oropharynx** is the part of the throat directly behind the mouth. It includes the soft part of the roof of the mouth (the soft palate), the base of the tongue, the tonsils and the back and side walls of the throat (see **Annex 1**).

- The **hypopharynx** is the lower part of the pharynx. It includes pyriform sinus, postcricoid region and the lateral, inferior and posterior pharynx wall (see **Annex 1**).
- The **larynx (or voicebox)** is the second most common place for HNC to develop(2). It is a short passageway formed by cartilage just below the pharynx in the neck. It contains the vocal cords and the epiglottis, which moves to cover the larynx to prevent food from entering the air passages. Larynx is divided by: supraglottis, glottis and subglottis.
- **Sinuses (maxillary, frontal, ethmoid and sphenoid sinuses)** are air spaces in the bones of the face alongside the nose and **nasal cavity** is the hollow space inside the nose.
- **Salivary glands** make saliva, which keeps the mouth moist. They are divided depending on their size as: minor salivary glands and major salivary glands (parotid, submandibular and sublingual glands).
- **Middle ear** can be the origin of HNC. It is made up of the eardrum and a cavity called the tympanum, which contains three little bones (the malleus, incus and stapes). These bones connect the eardrum to the inner ear. The tympanum is connected to the nasopharynx by a tube called the Eustachian tube.

Figure 1 shows a sagittal section of the head and neck where the mentioned topographic sites are visualized(3).

Head and Neck Cancer: Histopathology

Cancer is not just one disease, but a large group of almost 100 diseases. Its two main characteristics are uncontrolled growth of the cells in the human body and the ability of

these cells to migrate from the original site and spread to distant sites. If the spread is no controlled, cancer can result in death(4).

Now we will focus on a specific histological subtype, squamous cell neoplasm (SCN). SCN is the most common histological subtype of HNC, so when we talk about it, we are practically referring to almost 80 % of the tumours of head and neck(5).

SCN originates in the pluristratified squamous epithelium and it is diagnosed when malignant cells invade and disrupt the basement membrane (keratin[1] and desmosomes[2] could be seen under the microscope (**Figure 2**))(6).

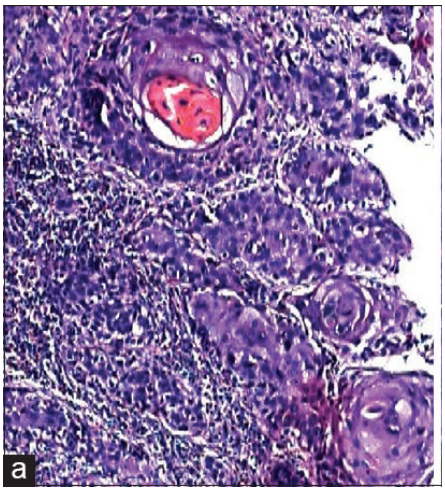


Figure 2. Moderately-differentiated squamous cell carcinoma (Grade II) showing keratin pearls and invasion of tumour cells in surrounding tissue(6).

Before the SNC appears, a series of changes or premalignant lesions can be visualized. They are (in order of the potential for malignant transformation): proliferative verrucous leucoplakia, erythroplasia, oral submucosal fibrosis, erythroleucoplakia, granular leucoplakia, laryngeal keratosis, actinic cheilosis, flat thick leucoplakia, red tongue of

[1]keratin: a scleroprotein that is the principal constituent of epidermis, hair, nails, horny tissues, and the organic matrix of the enamel of the teeth(4).

[2]Desmosome: a site of adhesion between two epithelial cells consisting, in each cell, of a dense attachment plaque with associated intermediate filaments and transmembrane proteins known as cadherin(4).

Plummer-Vinson syndrome, keratosis by snuff smokeless, lichen planus (erosive forms), thin flat leucoplakia(7).

Head and Neck Cancer: Diagnosis

Symptoms of a HNC will depend on where it is. Some examples would be(1,8):

- Oral cavity: an ulcer that does not heal within a few weeks; red or white patches on the gums, the tongue, or the lining of the mouth; pain; bleeding; tooth loss; dysphagia[3] or sore throat.
- Pharynx: dysphagia; sore throat; trouble breathing, speaking or hearing; headaches.
- Larynx: pain when swallowing or ear pain.
- Paranasal sinuses: unilateral epistaxis[4] and nasal obstruction.
- Nasal cavity: cervical lump, tinnitus[5], hearing loss, ear pain.
- Salivary glands: swelling in their location, paralysis of muscles in the face, pain in the face, the chin or the neck that does not disappear.

These patients require extensive history and physical examination with inspection (direct or indirect through mirrors or endoscopy) and palpation.

All diagnostic suspicions will be confirmed by pathological anatomy by biopsy or fine needle aspiration (FNA). Imaging tests help in tumour staging.

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[3]Dysphagia: difficulty in swallowing(4).

[4]Epistaxis: haemorrhage from the nose, usually due to rupture of small vessels overlying the anterior part of the cartilaginous nasal septum(4).

[5]Tinnitus: tinnitus is hearing ringing, buzzing, or other sounds without an external cause(4).

Head and Neck Cancer: Staging

Stage refers to the extent of your cancer, such as how large the tumour is, and if it has spread. It allows to understand as malignant is your tumour, chances of survival and the best treatment.

A cancer is always referred to by the stage it was given at diagnosis, even if it gets worse or spreads(8).

The staging of the different types of HNC are different between them but all of them use TNM staging system.

- T describes the size of the tumour.
- N describes how many lymph nodes are affected by cancer cells.
- M describes if the cancer has spread to another location of your body.

See **Annex 2** to know in a simple way the TNM staging of Head and Neck Tumours.

Head and Neck Cancer: Treatment

The main objective when trying to cure the cancer is to remove and destroy all tumour cells in your body. But we must take into account the importance of preserving the organ as well as realising therapy to rehabilitate the speech and swallowing to ensure an acceptable quality of life for the patient.

The choice of the treatment will depend on where the cancer is in the head or neck, the cancer staging and the tumour resectability. We have to consider the complexity of HNC treatment due to the large regional variability and anatomical limitations presented.

The treatment for early stage cancer is usually surgery and/or radiation therapy and for advanced cancer, a combination of chemotherapy and radiotherapy is usually required. Nasopharyngeal cancer is usually treated with chemo-radiotherapy in all stages(1).

Following, a simple treatment scheme is presented.

- Early stage cancer without lymph node involvement=stages I and II (see **Annex 2**): they are usually treated with surgery or radiotherapy.
- Loco-regionally advanced disease with lymph node involvement=stages III, Iva and IVb (see **Annex 2**): they can be treated with a combination therapy of surgery, radiotherapy and chemotherapy, depending on the characteristics of the disease.
- Disease with distant metastases=stage IVc and recurrent disease (see **Annex 2**): in cases of untreatable disease, palliative treatment can be applied with chemotherapy. On the other hand, in cases of relapse, the treatment varies depending on the pretreatment received and tumour characteristics.

Head and Neck Cancer: Epidemiology

HNCs are the seventh most common malignancy in the world with an estimated 686.328 new cancer cases diagnosed in 2012 (almost a 5% of all cancers) with a sex ratio of 2,96, being more frequent in males than females (**Figure 3:** lip, oral cavity, larynx, other pharynx and nasopharynx are included as HNC)(2). More than 90% of these cancers are squamous cell carcinomas(9). In terms of mortality, it is estimated that around 375.665 people died from HNC in 2012 (see **Figure 3**).

HNC incidence and mortality rates vary among countries, being the country with the highest incidence rate (ASR_W) combining lip and oral cavity, other pharyngeal and laryngeal cancer among males and females, Melanesia (29.3 and 17.0 respectively) followed by Central and Eastern Europe (22.8 and 3.2) and South-Central Asia (6.9 among females)(9).

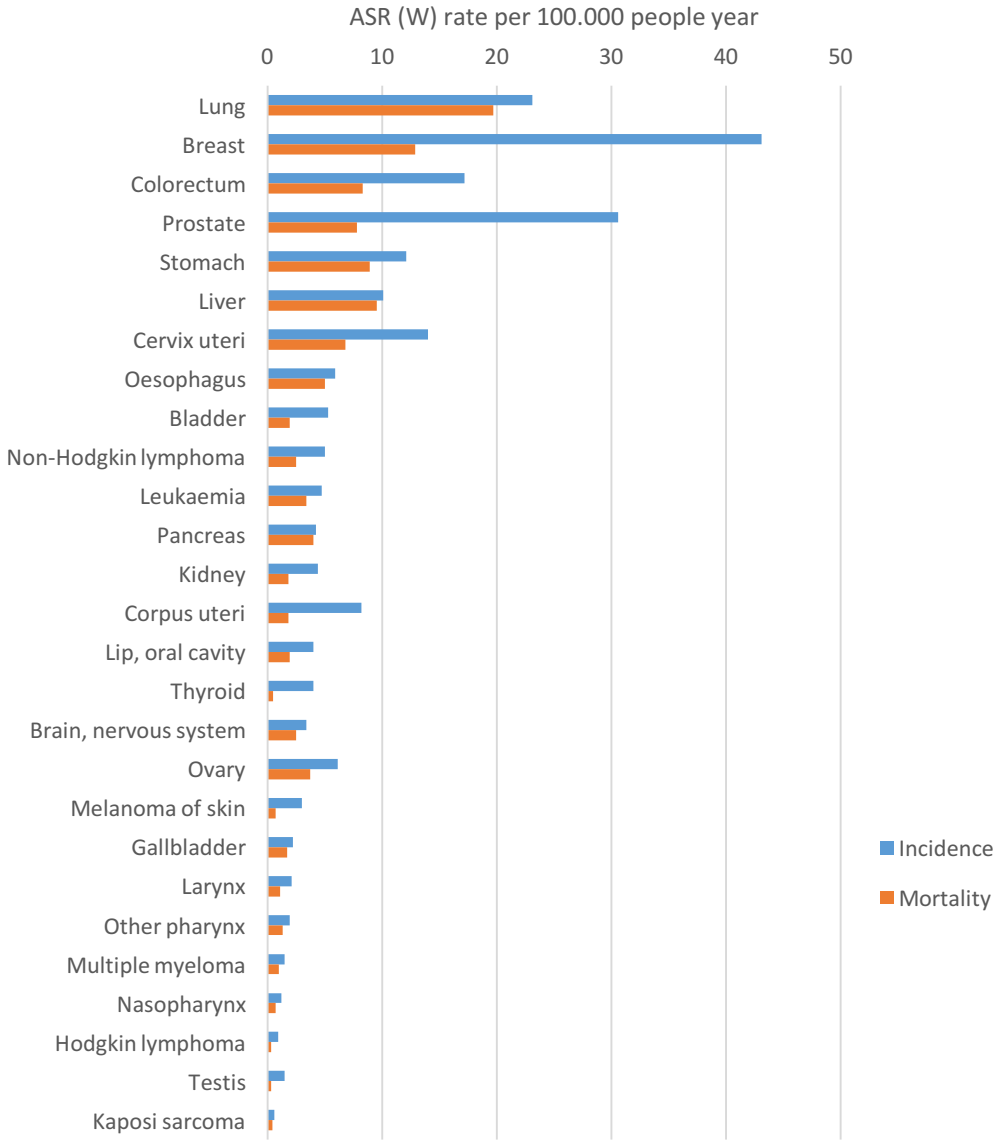


Figure 3. Estimated age-standardized incidence and mortality rates of HNC in world population ASR_w: Age-standardized to the world standard population rate(2).

Focusing on European incidence rates according to EUCAN (**Figure 4 and 5**), the highest incidence rate of HNCs is Hungary with 23.3 cases for lip, oral cavity and pharynx and 8.5 cases for the larynx per 100.000 inhabitants/year. The lowest is Cyprus with 2.7 cases per 100.000 inhabitants/year for lip, oral cavity and pharynx and, for the larynx, Iceland is the lowest with 1.0 cases per 100.000 inhabitants/year. The highest mortality rate is in Hungary for lip, oral cavity and pharynx with 12.5 and Moldova for the larynx with 4.7(10).

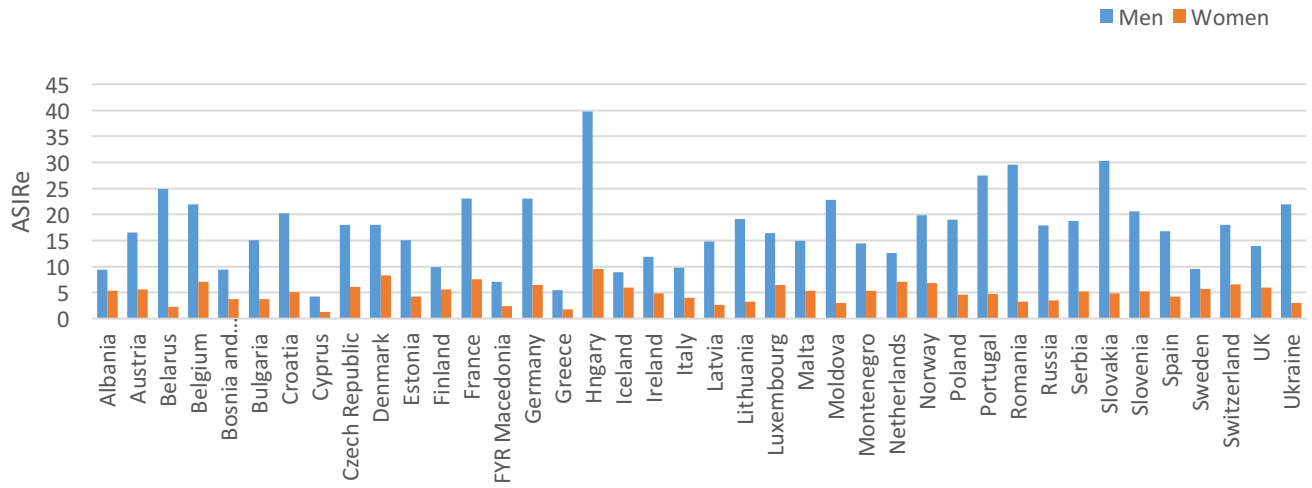


Figure 4. Estimated incidence from cancer of lip, oral cavity and pharynx in men and women, 2012; Age Standardised Rate (European) per 100.00(10).

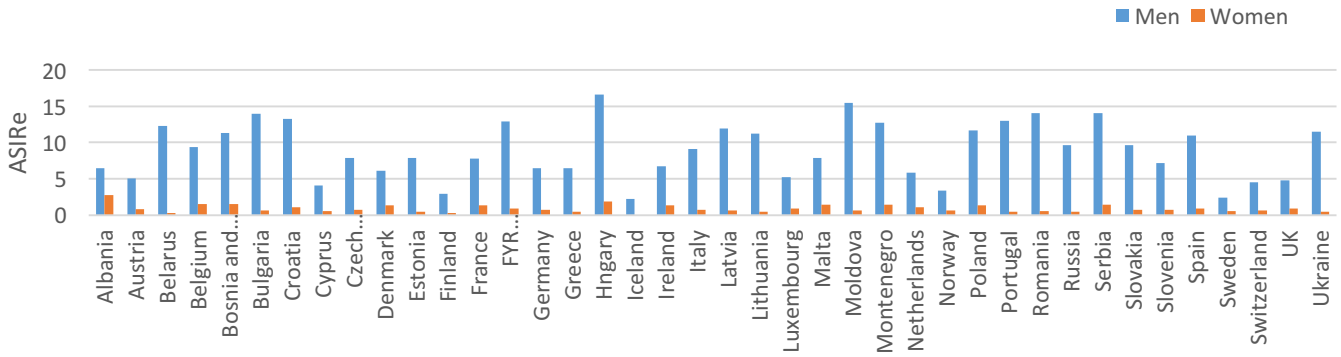


Figure 5. Estimated incidence from cancer of larynx in women and men, 2012; Age Standardised Rate (European) per 100.000(10).

For Spain, an estimated 9160 new cases were diagnosed in 2012 and 3391 people died, with a sex rate of 4,26 (being more frequent in males than in females). Girona, during the period from 2003 to 2007, did not get neither higher nor lower incidence rates among Spanish cancer registries, being Basque Country the region with the highest incidence rate of HNC and La Rioja which obtained the lowest(2,11).

Head and Neck Cancer: Risk Factors

A risk factor is known as any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury(12). Following, some risk factors of HNC are explained:

- Alcohol and tobacco use (includes not smoked consumption) are the main risk factors for HNC, with the exception of salivary gland cancers(13). At least 75 percent of HNC are caused by them. The addition of alcohol or tobacco to one of them increase enormously the risk of developing these cancers (a higher risk than the consumption of one of them alone)(14,15).
- Human papillomavirus (HPV), especially HPV-16, represents an important risk factor for some types of HNC. Special mention to oropharyngeal cancers that involve the tonsils or the base of the tongue(16). An example of how important it could be would be the increasing proportion in the United States of oral squamous cell carcinomas HPV related, while the incidence of oropharyngeal cancers related to other causes is falling. Perhaps this event can be explained due to a change in sexual behaviour in the last years(17).
- Epstein-Barr virus (EBV) is a risk factor for nasopharyngeal cancer(18). Some time ago the relation between EBV and salivary glands cancer was suspected but, nowadays this suspicion is questioned due to the appearance of new studies that deny the association(19,20).
- Paan (betel quid)[6]: Only three drugs (nicotine, ethanol and caffeine) are consumed more widely than betel. Paan is consumed more frequently in Southeast Asia and parts of the Pacific Rim. The habit of using paan in the mouth has been strongly associated with an increased risk of oral cancer(13).

- *Maté*[7] consumption has been implicated in many malignancies of different sites including the mouth, throat, oesophagus and larynx with a moderate to high risk(13).
- Preserved o salted food consumption at earlier age was associated with a higher risk of nasopharyngeal carcinoma independently of birthplace (this risk factor gets more significant in Chinese people due to their popular practices of weaning their babies on preserved foods and not because their ancestry)(21).
- Occupational exposure to wood or nickel dust are risk factors for nasopharyngeal, paranasal sinuses and nasal cavity cancers. Formaldehyde has a carcinogenic effect too (dose-dependent effect) for the aforementioned cancers(21). Additionally, people working in certain jobs in the construction, metal, textile, ceramic, logging and food industries may have an increased risk of cancer of the larynx(22).
- Poor oral health has been reported as a risk factor in the aetiology of HNC(23).
- Social factors as low socioeconomic status and low levels of education also seem to be related to disease development. By the other hand, this association may be due to an indirect effect, like for example, the fact that not having money keeps you from going to the dentist (so, that person will have a poor oral health, a reported risk factor for HNC)(21).

[6]Paan (betel quid): Commercially ready-made Paan mixtures of baked areca nut, slaked lime, spices, and tobacco extracts and concentrates; India(13).

[7]*Maté*: it is a tea-like beverage brewed from the dried leaves of the tree Ilex paraguarensis; South America(13).

- Gastroesophageal reflux has been associated with laryngeal and pharyngeal cancer regardless of age, gender, or tobacco and alcohol consumption(24).
- Radiation exposure. Radiation to the head and neck, for noncancerous conditions or cancer, is a risk factor for cancer of the salivary glands(25).
- Genetic predisposition may also play a role in these diseases, since there is a higher risk in those subjects with family history of HNC(26).

Fruit and vegetable intake have shown **a protective effect** (special attention to citrus fruit, which are rich in Vitamin C (an inhibitor of in vivo formation of nitrosamines), and orange-coloured vegetables, tomatoes and various dark green vegetables, all of which are rich in carotenoids)(21).

Tobacco: Impact on public health of Law 42/2010

2 years after the implementation of the Law 42/2010 (see **Annex 3**), it was possible to analyse the impact of the law in Spain. However, it was a relatively short time frame to fully assess the positive health effects of the modification made because, although it gave some immediate positive effects, most of the most significant effects are medium and long term. I will discuss briefly what impact it had on public health law 42/2010(27). In relation to exposure to environmental tobacco smoke (ETS), saying that the available results show that exposure to ETS in pubs, cafes and restaurants has been drastically reduced (nicotine concentrations and PM2.5 (suspended particles of less than 2.5 micros) decreased by more than 90%). It involves a considerable risk reduction to customers and workers that were exposed in this sector.

Regarding the prevalence, the National Health Survey of Spain 2011 show an overall reduction in tobacco consumption. The prevalence of current smokers is in 2011 of 27%

in adults aged 15 years and over compared to 29.9% in 2009 (16 and over). The prevalence of daily smokers has reduced from 26.2% in 2009 to 24% in 2011.

The higher consumption remains in the most disadvantaged classes in general, but has been reduced by certain groups as young adults, less educated, unemployed or who are studying. Among daily smokers, the number of cigarettes per day has fallen slightly.

In relation to the tobacco product sales, cigarette sales fell by 16.7% in 2011 and regarding the full year 2012, 2671 million cigarettes packs were sold, which is a 11.40% less than in 2011.

Regarding the morbidity associated, there has been a reduction in admission rates for acute myocardial infarction, ischemic heart disease and asthma in 2011, although further evaluation is necessary to know its specific impact on morbidity from these diseases.

Justification

HNC includes a large number of tumours located in different anatomical regions of the cervicofacial area, which, taken together, represent one of the most common cancers in the developed world, becoming into an important health problem today(2). Additionally, most of them are diagnosed in locally advanced stages, reducing, of this way, their range of treatment(24).

Recently, it has been shown that the incidence and survival of oropharyngeal tumours have increased in some countries such as USA. Subsequent investigations showed that these tumours were associated with HPV but not to the tobacco and alcohol consumption(17,28).

Knowing if HPV is involved or not in the oropharyngeal tumour histopathology of our patients could have an impact in our health system by increasing or decreasing the aggressiveness of the treatment. HPV vaccines could be a good alternative for the prevention of these tumours too.

Due to the epidemiological impact of HNC in our country and the importance of knowing if Girona has an increasing number of diagnoses of oropharyngeal tumours associated with HPV, I thought it appropriate to analyse the incidence and the survival of HNC and its different topographic sites in Girona province during the period of 1994 to 2013, using the database of the Girona Cancer Registry (GCR).

Moreover, this project would also help to update the GCR database for future investigations.

HYPOTHESES

1) Head and Neck Cancer (HNC) had a different incidence according to age and sex of the population from Girona province during 1994 to 2013.
2) The most frequent topographic site of HNC in Girona during the period of the study (1994-2013) was different by age and sex.
3) Squamous cell neoplasms were the most frequent histological type for both sexes and all ages.
4) The incidence of HNC in Girona has decreased significantly during the period of the study (1994-2013) perhaps due to the measure adopted to control the smoking habit in Spain.
5) The incidence of Oropharynx Cancer increased during the period of the study (1994-2013) as opposed of HNC in general (like occurs in USA due to the association with HPV).
6) HNC survival in Girona during the period of this study (1994-2013), is different according to sex and topographic site of HNC.

OBJECTIVES

In order to prove whether the above hypotheses can be confirmed, the following aims were planned:

1,2,3) Estimate the incidence of patients diagnosed with HNC during the period 1994-2013 in Girona by sex, age, topographic site of HNC, and some of the most prevalent histological types.

4) Analyse the incidence trend of HNC in Girona province from 1994 to 2013.

5) Determine the incidence trend of Oropharynx Cancer and compare the results with those of USA studies.

6) Calculate the observed survival of HNC by sex and topographic site of HNC during the period 1994-2013 in Girona.

DATA AND METHODS

Data

The database used in this final degree project was obtained from the Girona Cancer Registry (GCR). The GCR is a population-based cancer registry located in the northeast of Catalonia and it covers 753.054 residents in Girona province according to the census of 2015 provided by *l'Institut d'Estadística de Catalunya* (IDESCAT)(29). Following, population pyramid from the census of 2015 is shown (**Figure 6**).

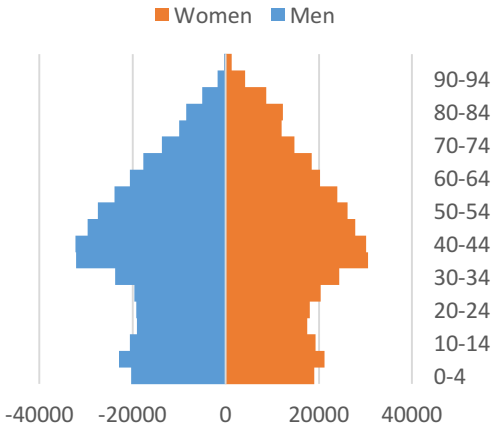


Figure 6. Population pyramid from Girona in 2015(29).

The main objective of the GCR is to register new cases of cancer diagnosed each year to the residents of Girona (inside and outside of the province) and to obtain, thanks to this registry, epidemiological indicators of a cancer diagnosed in Girona, allowing the impact of cancer in the population to be evaluated and controlled. Thanks to this population-based cancer registry, incidence, survival and mortality analysis of a determined neoplasm can be realized.

In order to keep updated the registry, information sources are neccesary:

- Hospital discharges of the Girona province hospitals.
- Haematology and pathological anatomy laboratory results (cytology, biopsy), together with laboratory results (cytogenetics and molecular biology) of another reference centres located outside of the province. If microscopical verification is not possible, the GCR will register the neoplasms diagnosed by exploratory techniques (clinical or surgical, imaging techniques or laboratory).

- Death Certificate Only[8] (DCO) of patients that only this information is provided.

Due to the nature of all this information, confidentiality agreement is necessary according to the *Ley orgánica 15/1999, 13 diciembre, de protección de datos de Carácter Personal*(30).

Additionally, this study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki(31).

All cases included in the GCR are registered following a series of recommendations of the European Network for Cancer Registries (ENCR) and they are coded by topographic sites and by morphology using the International Classification of Diseases for Oncology, third edition (ICD-O-3)(32).

To accomplish this final degree project, cases were selected of the database of the GCR. Only patients with HNC with an *in situ* and invasive behaviour from Girona province during the period 1994-2013 were selected and, specifically, the tumours with the following codes of the ICD-O-3 were used: C00-C14; C30-C32. Head, face or neck, NOS (not otherwise specified) with the code C76.0 was excluded (see **Annex 1**).

[8]Death Certificate Only (DCO): Percentage of DCOs is a measure of quality in a population-based cancer registry and is recommended to remain low(33).

These codes were divided by large areas:

Lips	C00
Oral cavity	C01, C02, C03, C04, C05, C06
Salivary glands	C07, C08
Oropharynx	C09, C10
Nasopharynx	C11
Hypopharynx	C12, C13
Not specified pharynx	C14
Nose, ear and sinus	C30, C31
Larynx	C32

The most incident histological subtypes of HNC were grouped too to study their sex and topographic site distribution. They were: squamous cell neoplasms (SCN), undifferentiated carcinoma (UC), adenomas and adenocarcinomas(AAA), mucoepidermoid neoplasms(MN) and acinar cell neoplasms(ACN). Following, grouped histological subtypes of HNC used in this study and their corresponding morphologic codes (see **Annex 1**):

Squamous cell neoplasms	8050-8084
Undifferentiated carcinoma	8020
Adenomas and adenocarcinomas	8140-8384
Mucoepidermoid neoplasms	8430
Acinar cell neoplasms	8550-8552

After analysing and debugging the database, a series of quality indicators were established.

Table 1.
Quality indicators of primary Head and Neck tumours registered in GCR, Girona (Spain) 1994-2013.

Quality indicators	
Microscopical verification (MV)	**97,5%**
• **Clinical confirmation only** • **Clinical investigation** • **Surgical exploration** • **Specific tumours markers**	**0,6%** **0,8%** **0%** **0%**
Death certificate only (DCO)	1,1%
Without year of birth (N)	0,1% (3)
Completeness	94,7%

N, number of patients.

Statistical analysis

To accomplish this final degree project, descriptive analyses were performed and incidence rates, trends in incidence rates and survival rates have been estimated.

Incidence of HNC of Girona province during the period 1994-2013 was estimated globally and according to the topographic site of the tumour. The prognostic variables used in this project were age, year of diagnosis and sex.

The population of Girona province was provided by the *Institut d'Estadística de Catalunya* (IDESCAT) to calculate incidence rates(29). Incidence was estimated as crude rate[9] (CR), age-standardized to the European standard population rate[10] (ASR_E) and age-specific rate[11].

[9]Crude Rate (CR): crude rates are calculated using a simple formula in which the number of cases is divided by the corresponding population and multiplied by 100.000.

The age-standardized rates were performed using the "direct method", which is used when we have a large denominator (in our case the population of Girona) and the frequency of events is not too reduced to get unstable rates. This method consists in applying specific rates for each stratum of the confounding variable (age, social class...) of the populations whose rates will be compared to a standard population divided into the same strata or categories. The major advantage of using the "direct method" is that it allows to create comparable adjusted rates thanks to the use of an identical standard population (in this case the European standard population)(34).

Epidat software was used to compute CR and ASR_E with the 95% CI and they were expressed in 100.000 inhabitants per year(35). Age-specific rate was calculated by stratifying the age into 18 groups of 5 years each, the results were expressed in 100.000 inhabitants per year too.

Joinpoint statistical software was used to quantify the evolution of incidence, as the annual percentage change (APC) and to evaluate changes in trends over time(36). Only incidence trend of HNC and Oropharynx cancer were calculated in this study.

[10]Adjusted Rate: a fictitious summary rate statistically adjusted to remove the effect of a variable, such as age or sex, to permit unbiased comparison between groups having different compositions with respect to these variables(4).

[11]Specific Rate: a rate that applies to a specific demographic subgroup, e.g., individuals of a specific age, sex, or race, giving the total number of events in relation only to that subgroup(4).

Mean age and standard deviation (SD) were calculated for HNC and the observed survival in men and women, and the *t* test was used for comparisons. Median age and its standard deviation (SD) were calculated too for the same groups. Differences between sex were examined using X^2 for qualitative variables such age groups, histological subtypes, topographic site of HNC and behaviour of the tumour.

Considering survival analyses, DCO and cases diagnosed by autopsy were excluded from the study population. Patient were followed from date of diagnosis to date of death (no cancer-specific death due to information on cause of death was not available for the Spanish population) or end of follow-up (31st December 2014), whichever came first. Ten-year crude HNC survival was estimated using the Kaplan-Meier method and observed survival was calculated by stratifying by sex and topographic site of HNC. Statistical differences between curves were assessed using the log-rank test.

Statistical significance was determined at p <0.05 for all analyses. Analyses were performed with SPSS version 23.

RESULTS

Descriptive epidemiology

3171 cases of HNC were identified in the GCR database during the period 1994-2013. Among these cases, 2630 were men (82.9%) and 541 were women (17.1%). Most part of the selected cases, 3062, had an invasive behaviour (96.6%), the remainder, 109, had *in situ* behaviour (3.4%). Of all these cases, 2547 were SCN (80.3%), 53 AAA (1.7%), 30 UC (0.94%), 25 MN (0.78%), 20 ACN (0.63%) and the remainder, 496, were part of several histological subtypes less incidents (15.6%).

Table 2 shows topographic sites of the most incident histological types of HNC in Girona 1994-2013. We can observe some differences between men and women in the distribution of SCN, the larynx is the topographic site preferred in men in contrast of the oral cavity in women. Other difference would be the distribution of AAA, nose, ear and sinus were the preferred areas in men and salivary glands in women. The most frequent topographic site of UC was nasopharynx for both sexes(37).

Table 2. Topographic sites of the most incident histological types of HNC in Girona 1994–2013.

	SCN		UC		AAA		MN		ACN	
	Men N (%)	Women N (%)	Men N (%)	Women N (%)	Men N (%)	Women N (%)	Men N (%)	Women N (%)	Men N (%)	Women N (%)
Lips (C00)	335 (15.15)	56 (16.66)	0 (0.00)	0 (0.00)	0 (0.00)	1 (4.54)	1 (7.1)	0 (0.00)	0 (0.00)	0 (0.00)
Oral cavity (C01; C02; C03; C04; C05; C06)	513 (23.20)	**169 (50.29)**	2 (9.0)	0 (0.00)	5 (16.12)	7 (31.81)	3 (21.4)	5 (45.4)	0 (0.00)	1 (9.0)
Salivary glands (C07; C08)	20 (0.90)	7 (2.08)	1 (4.5)	2 (25)	5 (16.12)	**10 (45.45)**	**8 (57.1)**	**6 (54.5)**	**9 (100)**	**10 (90.9)**
Oropharynx (C09; C10)	201 (9.09)	24 (7.14)	2 (9.0)	0 (0.00)	1 (3.22)	0 (0.00)	1 (7.1)	0 (0.00)	0 (0.00)	0 (0.00)
Nasopharynx (C11)	58 (2.62)	14 (4.16)	**11 (50)**	**5 (62.5)**	0 (0.00)	0 (0.00)	1 (7.1)	0 (0.00)	0 (0.00)	0 (0.00)
Hypopharynx (C12; C13)	212 (9.58)	9 (2.67)	2 (9.0)	0 (0.00)	2 (16.12)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
NE Pharynx (C14)	33 (1.49)	4 (1.19)	0 (0.00)	0 (0.00)	1 (3.22)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Nose, ear and sinus (C30; C31)	26 (1.17)	14 (4.16)	3 (13.6)	0 (0.00)	**16 (51.61)**	4 (18.18)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Larynx (C32)	**813 (36.77)**	39 (11.60)	1 (4.5)	1 (12.5)	1 (3.22)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

N: number of cases; NE: not specified; SCN, Squamous cell neoplasms; UC, Undifferentiated carcinoma; AAA, Adenomas and adenocarcinomas; MN, Mucoepidermoid neoplasms; ACN, Acinar cell neoplasms.
Bold values denote more frequent.

Table 3. Summary of the descriptive epidemiology by sex, Girona 1994-2013.

	Men	Women	Total	P-value[1]
N (%)	2630 (82.9)	541 (17.1)	3171 (100)	
Mean age (SD)	63 (13.0)	67.49 (15.9)	63.7 (13.6)	p<0.001
Median age (min-max)	63 (16-100)	71 (5-97)	64 (5-100)	
CR	41.0	8.4	24.7	
ASR_E	50.0	8.9	28.4	
Age groups, years N (%)				p<0.001
0-24	8 (0.3)	7 (1.3)	15 (0.5)	
25-49	392 (14.9)	71 (13.1)	463 (14.6)	
50-74	1682 (64.0)	249 (46.1)	1931 (61.0)	
75-+85	546 (20.8)	213 (39.4)	759 (24.0)	
Histological subtypes N (%)				p<0.001
SCN	2211 (84.1)	336 (62.1)	2547 (80.3)	
AAA	31 (1.2)	22 (4.1)	53 (1.7)	
UC	22 (0.83)	8 (1.4)	30 (0.94)	
Others	366 (13.9)	175 (32.3)	541 (17.0)	
Topographic site N (%)				p<0.001
Lips	375 (14.2)	95 (17.5)	470 (14.8)	
Oral cavity	571 (21.7)	196 (36.2)	767 (24.2)	
Salivary glands	70 (2.6)	77 (14.2)	147 (4.6)	
Oropharynx	247 (9.39)	47 (8.6)	294 (9.3)	
Nasopharynx	93 (3.5)	31 (5.7)	124 (3.9)	
Hypopharynx	230 (8.7)	10 (1.8)	240 (7.6)	
NE pharynx	40 (1.5)	5 (0.92)	45 (1.4)	
Nose, ear and sinus	77 (2.9)	35 (6.4)	112 (3.5)	
Larynx	927 (35.24)	45 (8.3)	972 (30.7)	
Behaviour N (%)*				p=0.026
In situ	99 (3.8)	10 (1.8)	109 (3.4)	
Invasive	2531 (96.2)	531 (98.2)	3062 (96.6)	

N, number of cases; SD, standard deviation; CR, crude rate per 100,000 inhabitants/year; ASR_E, age-specific rate for the European standard population; SCN, squamous cell neoplasms; AAA, adenomas and adenocarcinomas; UC, undifferentiated carcinoma; NE, not specified.
[1] P value = T Student test for Mean Age / Chi-square test for Age groups, Histological subtypes, Topographic site and Behaviours.
*Only *in situ* and invasive were selected in this study.

Table 3 summarizes some aspects of the descriptive epidemiology by sex of the cases of the GCR database during the period 1994-2013. It shows us the median age of diagnose of men (63) and women (67.4), those median ages explain why age group of 50 to 74

years was the most frequent for both sexes. We can observe the distribution of HNC between topographic sites too and if we compare which topographic site had a major number of cases in men and women, we realize that in men was the larynx but in women was oral cavity. SCN was the most frequent for both sexes. For more information about descriptive epidemiology, **Annex 4** may be consulted.

Incidence

Table 4 summarizes the incidence of HNC and their topographic sites, grouped into 5-years periods (except the first period 1994-1997, which was only 4 years). To explain the incidence trends, the APC in incidence rates of HNC and Oropharynx cancer are shown in **Table 5.**

Table 4. Head and Neck Cancer incidence by time periods in each and both sexes in Girona 1994–2012.

Topographic site	Period of time	Men				Women				Both sexes			
		N	CR	$ASIR_E$	CI95%	N	CR	$ASIR_E$	CI95%	N	CR	$ASIR_E$	CI95%
Head and Neck (C00-C14; C30-C32)	1994–1997	538	**51,4**	61,6	[56,4; 67,2]	77	**7,2**	7,9	[6,2; 10,0]	615	**29,1**	33,8	[31,2; 36,7]
	1998–2002	640	**46,4**	55,5	[51,2; 60,1]	121	**8,6**	8,8	[7,3; 10,6]	761	**27,3**	30,8	[28,6; 33,1]
	2003–2007	661	**40,5**	50,5	[46,6; 54,6]	148	**9,1**	9,5	[8,0; 11,3]	809	**24,9**	28,8	[26,8; 30,9]
	2008–2012	661	**34,8**	43,2	[39,9; 46,7]	157	**8,4**	8,8	[7,4; 10,3]	818	**21,8**	25,1	[23,3; 26,9]
Lips	1994–1997	75	**7,1**	9,2	[7,2; 11,8]	11	**1,0**	1,0	[0,52; 2,0]	86	**4,0**	4,8	[3,8; 6,0]
	1998–2002	107	**7,7**	9,9	[8,0; 12,0]	30	**2,1**	2,0	[1,4; 3,0]	137	**4,9**	5,6	[4,7; 6,6]
	2003–2007	100	**6,1**	8,1	[6,6; 10,0]	23	**1,4**	1,4	[0,92; 2,2]	123	**3,7**	4,4	[3,6; 5,2]
	2008–2012	76	**4,0**	5,3	[4,2; 6,7]	25	**1,3**	1,3	[0,90; 2,0]	101	**2,6**	3,1	[2,5; 3,8]
Oral cavity	1994–1997	112	**10,7**	12,8	[10,5; 15,6]	31	**2,9**	3,2	[2,2; 4,6]	143	**6,7**	8,0	[6,7; 9,4]
	1998–2002	120	**8,7**	10,1	[8,4; 12,3]	41	**2,9**	3,0	[2,1; 4,1]	161	**5,7**	6,4	[5,5; 7,5]
	2003–2007	140	**8,5**	10,4	[8,7; 12,3]	50	**3,1**	3,2	[2,3; 4,2]	190	**5,8**	6,7	[5,7; 7,7]
	2008–2012	164	**8,6**	10,6	[9,0; 12,4]	60	**3,2**	3,3	[2,5; 4,2]	224	**5,9**	6,8	[5,9; 7,7]
Salivary glands	1994–1997	16	**1,5**	2,1	[1,1; 3,7]	16	**1,4**	1,6	[0,94; 2,7]	32	**1,5**	1,9	[1,2; 2,7]
	1998–2002	14	**1,0**	1,2	[0,63; 2,1]	19	**1,3**	1,4	[0,85; 2,2]	33	**1,1**	1,3	[0,89; 1,8]
	2003–2007	11	**0,67**	0,88	[0,41; 1,67]	22	**1,3**	1,4	[0,89; 2,2]	33	**1,0**	1,1	[0,76; 1,6]
	2008–2012	22	**1,1**	1,5	[0,93; 2,3]	16	**0,86**	0,85	[0,50; 1,4]	38	**1,0**	1,1	[0,81; 1,6]
Oropharynx	1994–1997	47	**4,4**	5,3	[3,9; 7,3]	4	**0,37**	0,40	[0,1; 1,0]	51	**2,4**	2,7	[2,0; 3,7]
	1998–2002	56	**4,0**	4,7	[3,5; 6,2]	7	**0,50**	0,49	[0,2; 1,0]	63	**2,2**	2,5	[1,9; 3,2]
	2003–2007	53	**3,2**	3,7	[2,8; 5,0]	13	**0,80**	0,88	[0,46; 1,5]	66	**2,0**	2,2	[1,7; 2,9]
	2008–2012	66	**3,4**	4,2	[3,2; 5,4]	16	**0,86**	0,97	[0,56; 1,5]	82	**2,1**	2,5	[2,0; 3,2]
Nasopharynx	1994–1997	21	**2,0**	2,1	[1,3; 3,4]	2	**0,18**	0,22	[0; 0,88]	23	**1,0**	1,1	[0,71; 1,7]
	1998–2002	22	**1,5**	1,7	[1,0; 2,6]	5	**0,35**	0,37	[0,1; 0,92]	27	**0,97**	1,0	[0,69; 1,5]
	2003–2007	22	**1,3**	1,3	[0,86; 2,2]	15	**0,93**	0,90	[0,47; 1,5]	37	**1,1**	1,1	[0,80; 1,6]
	2008–2012	24	**1,2**	1,4	[0,87; 2,1]	8	**0,43**	0,47	[0,2; 0,95]	32	**0,85**	0,94	[0,64; 1,3]
Hypopharynx	1994–1997	48	**4,5**	5,6	[4,1; 7,6]	2	**0,18**	0,20	[0; 0,82]	50	**2,3**	2,7	[2,0; 3,7]
	1998–2002	59	**4,2**	4,9	[3,7; 6,5]	0	**0**	0	-	59	**2,1**	2,4	[1,8; 3,1]
	2003–2007	53	**3,2**	3,9	[2,9; 5,2]	6	**0,37**	0,39	[0,15; 0,87]	59	**1,8**	2,1	[1,6; 2,8]
	2008–2012	60	**3,1**	3,7	[2,8; 4,8]	1	**0,05**	0,06	[0, 0,37]	61	**1,6**	1,8	[1,4; 2,4]
NE Pharynx	1994–1997	8	**0,76**	0,86	[0,37; 1,9]	2	**0,18**	0,23	[0; 0,90]	10	**0,47**	0,54	[0,21; 1,0]
	1998–2002	8	**0,58**	0,65	[0,25; 1,4]	1	**0,07**	0,06	[0; 0,47]	9	**0,32**	0,36	[0,15; 0,74]
	2003–2007	13	**0,79**	0,98	[0,51; 1,7]	2	**0,12**	0,11	[0; 0,50]	15	**0,46**	0,52	[0,28; 0,88]
	2008–2012	9	**0,47**	0,62	[0,26; 1,2]	0	**0**	0	-	9	**0,23**	0,27	[0,1; 0,53]
Nose, ear and sinus	1994–1997	17	**1,6**	1,8	[1,0; 3,1]	4	**0,37**	0,41	[0,1; 1,1]	21	**0,99**	1,1	[0,68; 1,7]
	1998–2002	17	**1,2**	1,4	[0,81; 2,5]	9	**0,64**	0,63	[0,26; 1,2]	26	**0,93**	0,98	[0,61; 1,4]
	2003–2007	17	**1,0**	1,2	[0,71; 2,1]	10	**0,62**	0,66	[0,30; 1,2]	27	**0,83**	0,97	[0,61; 1,4]
	2008–2012	24	**1,2**	1,5	[0,97; 2,3]	9	**0,48**	0,44	[0,15; 0,88]	33	**0,87**	1,0	[0,68; 1,4]
Larynx	1994–1997	190	**18,1**	21,7	[18,6; 25,2]	4	**0,37**	0,39	[0,1; 1,0]	194	**9,1**	10,5	[9,0; 12,1]
	1998–2002	226	**16,3**	19,6	[17,1; 22,5]	7	**0,50**	0,57	[0,20; 1,1]	233	**8,3**	9,5	[8,4; 10,9]
	2003–2007	242	**14,8**	18,8	[16,5; 21,4]	6	**0,37**	0,40	[0,15; 0,92]	248	**7,6**	9,0	[8,0; 10,2]
	2008–2012	211	**11,1**	13,7	[11,9; 15,8]	22	**1,18**	1,31	[0,81; 2,0]	233	**6,2**	7,2	[6,3; 8,2]

N: number of cases; CR: crude rate; $ASIR_E$: European age standardized rate; NE: not specified.

Table 5. Number of cases (N) and annual percentage of change (APC) in incidence rates of Head and Neck Cancer in Girona 1994–2013.

Topographic site	Men			Women			Both sexes		
	N	APC	(lower CI; upper CI) p value	N	APC	(lower CI; upper CI) p value	N	APC	(lower CI; upper CI) p value
Head and Neck tumours	**2628**	**-2.5**	**(-3.1; -2.0) p<0.01**	540	0.8	(-0.4; 2.1) p=0.2	**3168**	**-2.0**	**(-2.5; -1.5) p<0.01**
Oropharynx tumours	247	-0.8	(-2.9; 1.4) p=0.4	47	3.7	(-1.2; 9.0) p=0.1	294	0.1	(-2.0; 2.3) p=0.9

Bold values denote statistically significant.

For the whole period 1994-2013, HNC incidence decreased significantly in both sexes and in men, with an APC of -2.0 and -2.5 respectively. In contrast, HNC incidence increased in women, with an APC of 0.8 but it was not statistically significant. Oropharyngeal tumours incidence did not increase significantly over the entire period, even when the analysis was performed for both sexes either together or separately. **Figure 7** and **Figure 8** show graphics of the incidence trend of HNC and the incidence trend of Oropharyngeal tumours respectively. The asterisk indicates significant APC.

Figure 7. Incidence trend of Head and Neck Cancer by sex in the period 1994-2013 in Girona.

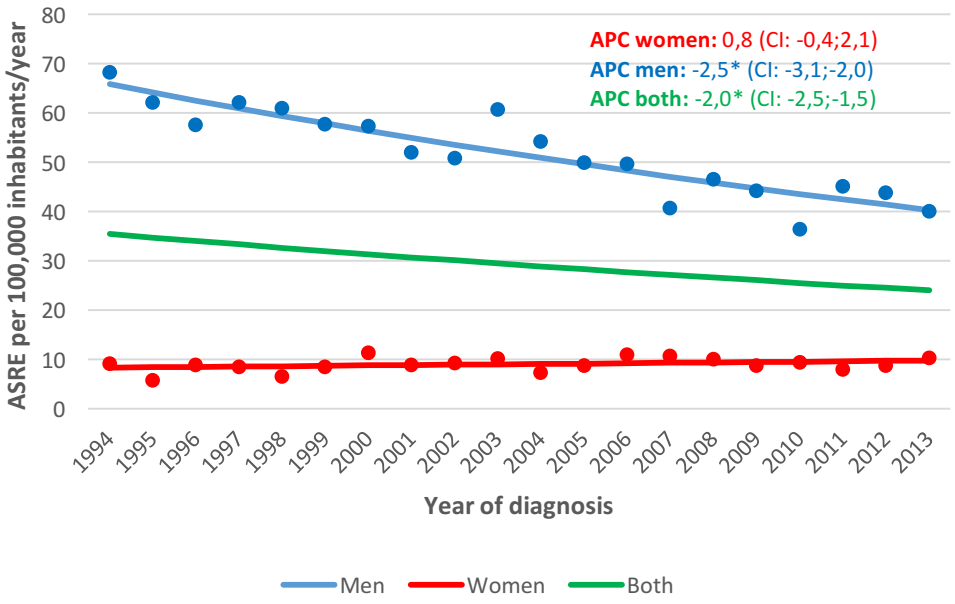
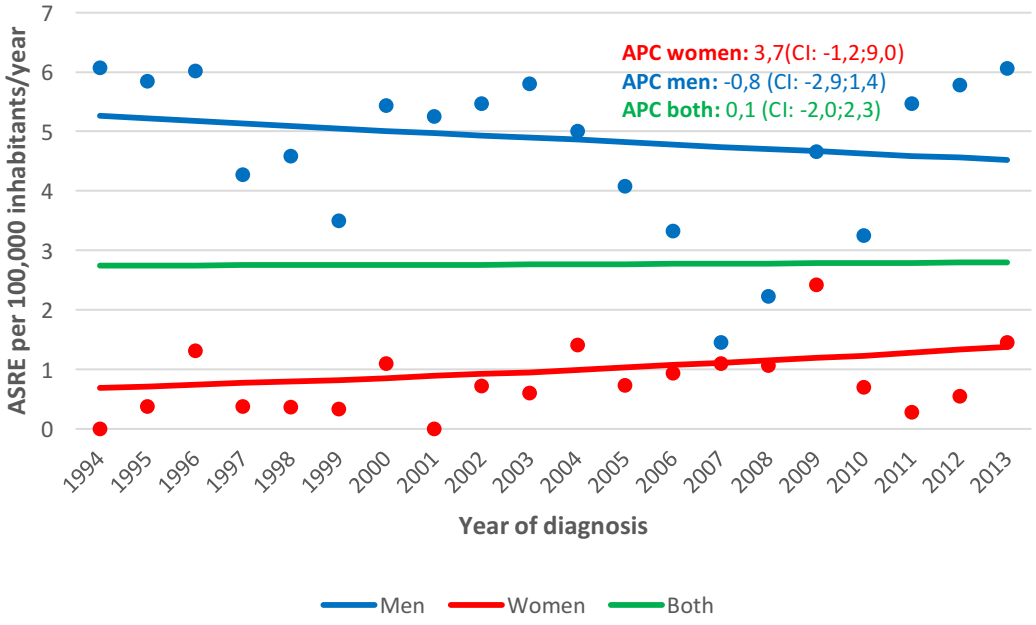
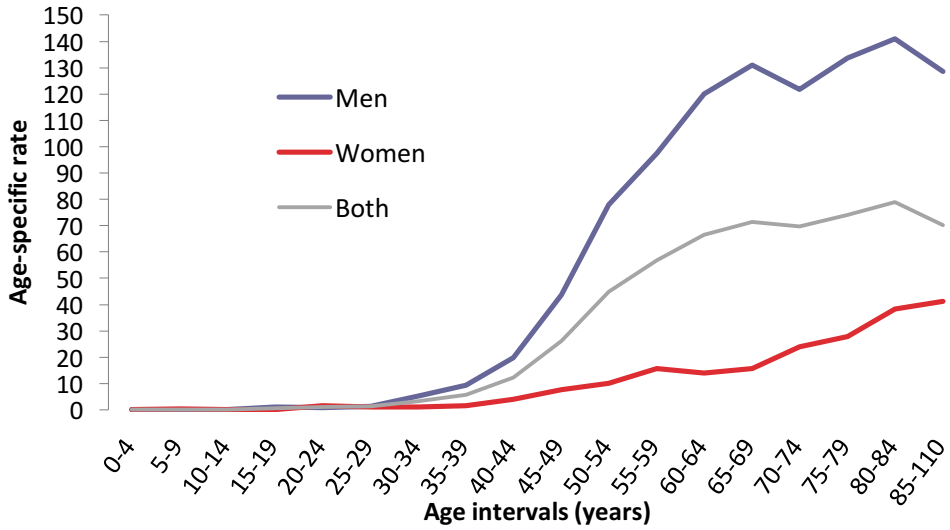


Figure 8. Incidence trend of Oropharyngeal tumours by sex in the period 1994-2013 in Girona.



Regarding HNC age-specific rates, **figure 9** shows them divided by age. We can observe that after 40 years, the incidence was much higher and it did not diminish in subsequent years. Number of cases in men were much higher than in women (as we mentioned above).

Figure 9. Incidence of Head and Neck Cancer by age, Girona 1994-2013.



Survival

OS at 3, 5 and 10 years for the different topographic sites of HNC are shown in **Table 6.** Hypopharyngeal and NE Pharyngeal tumours in women were not analysed because of the small number of patients at risk. The best OS for both sexes was in nasopharyngeal tumours (maybe due to a more effective treatment) with a 73.8%, 63.9% and 54.9% at 3, 5 and 10 years respectively. In opposition to this, the worst OS (discounting unanalysed) for both sexes was found in oropharyngeal tumours with a 44.8%, 35.8% and 21.3% at 3, 5 and 10 years respectively.

Table 6. Observed survival (OS) of Head and Neck Cancer for each and both sexes in Girona 1994–2013.

		Men		Women		Both sexes	
		N	OS (95%CI)	N	OS (95%CI)	N	OS (95%CI)
Head and Neck Cancer	**3 years**	1313	57.2 (55.2-59.1)	312	67.4 (63.2-71.5)	1623	58.9 (57.1-60.6)
	5 years	990	48.3 (46.3-50.2)	235	59.7 (55.3-64.0)	1223	50.2 (48.4-51.9)
	10 years	484	33.5 (31.3-35.6)	115	45.4 (40.5-50.3)	596	35.5 (33.5-37.4)
Lips	**3 years**	291	85.2 (81.4-88.9)	81	90.2 (84.1-96.2)	371	86.2 (83.0-89.3)
	5 years	231	73.3 (68.5-78.0)	62	81.6 (73.3-89.8)	290	75.0 (70.8-79.1)
	10 years	115	50.2 (44.5-55.8)	23	48.4 (35.8-60.9)	137	50.1 (45.0-55.1)
Oral cavity	**3 years**	238	48.5 (44.1-52.8)	89	56.8 (49.5-64.0)	326	50.6 (46.8-54.3)
	5 years	165	39.7 (35.3-44.0)	70	50.7 (43.2-58.1)	234	42.4 (38.6-46.1)
	10 years	69	25.1 (20.7-29.4)	35	40.6 (32.5-48.6)	104	28.8 (24.8-32.7)
Salivary glands	**3 years**	37	59.9 (47.9-71.8)	24	68.3 (57.7-78.8)	83	64.5 (56.6-72.3)
	5 years	26	52.2 (39.6-64.7)	40	59.5 (48.1-70.8)	66	56.2 (47.7-64.6)
	10 years	15	35.6 (22.2-48.9)	29	51.5 (39.7-63.2)	44	45.0 (36.1-53.8)
Oropharynx	**3 years**	76	40.0 (33.5-46.4)	27	69.8 (55.8-83.7)	103	44.8 (38.7-50.8)
	5 years	50	31.9 (25.4-38.3)	19	55.9 (40.4-71.3)	69	35.8 (29.7-41.8)
	10 years	18	17.0 (10.9-23.0)	10	43.3 (25.8-60.7)	26	21.3 (15.2-27.3)
Nasopharynx	**3 years**	60	71.9 (62.4-81.3)	22	79.7 (65.1-94.2)	82	73.8 (65.9-81.6)
	5 years	47	64.0 (53.8-74.1)	15	63.4 (44.9-81.8)	61	63.9 (54.8-72.9)
	10 years	28	52.6 (41.2-63.9)	15	63.4 (44.9-81.8)	35	54.9 (44.9-64.8)
Hypopharynx	**3 years**	67	33.3 (27.0-39.5)	*	*	69	33.5 (27.4-39.5)
	5 years	51	26.7 (20.8-32.5)	*	*	52	26.6 (20.7-32.4)
	10 years	20	15.6 (10.3-20.8)	*	*	21	15.8 (10.5-21.0)
NE Pharynx	**3 years**	16	43.4 (27.7-59.0)	*	*	20	47.6 (32.9-62.3)
	5 years	8	25.6 (11.2-39.9)	*	*	12	32.3 (17.9-46.6)
	10 years	2	7.7 (0.00-17.5)	*	*	4	13.7 (2.1-25.2)
Nose, ear and sinus	**3 years**	31	43.8 (32.4-55.1)	12	41.3 (24.4-58.1)	43	42.9 (33.4-52.3)
	5 years	24	37.7 (26.5-48.8)	12	41.3 (24.4-58.1)	35	38.6 (29.1-48.0)
	10 years	14	31.7 (20.3-43.0)	3	24.6 (5.7-41.4)	14	29.7 (19.9-39.5)
Larynx	**3 years**	503	61.5 (58.3-64.6)	26	74.4 (61.2-87.5)	529	62.1 (58.9-65.2)
	5 years	395	53.0 (49.6-56.3)	16	70.1 (55.2-84.9)	411	53.8 (50.4-57.1)
	10 years	210	39.3 (35.7-42.8)	10	58.4 (38.9-77.8)	219	40.0 (36.4-43.5)

NE, not specified; N, patients at risk; OS, observed survival.
*, number of cases were insufficient.

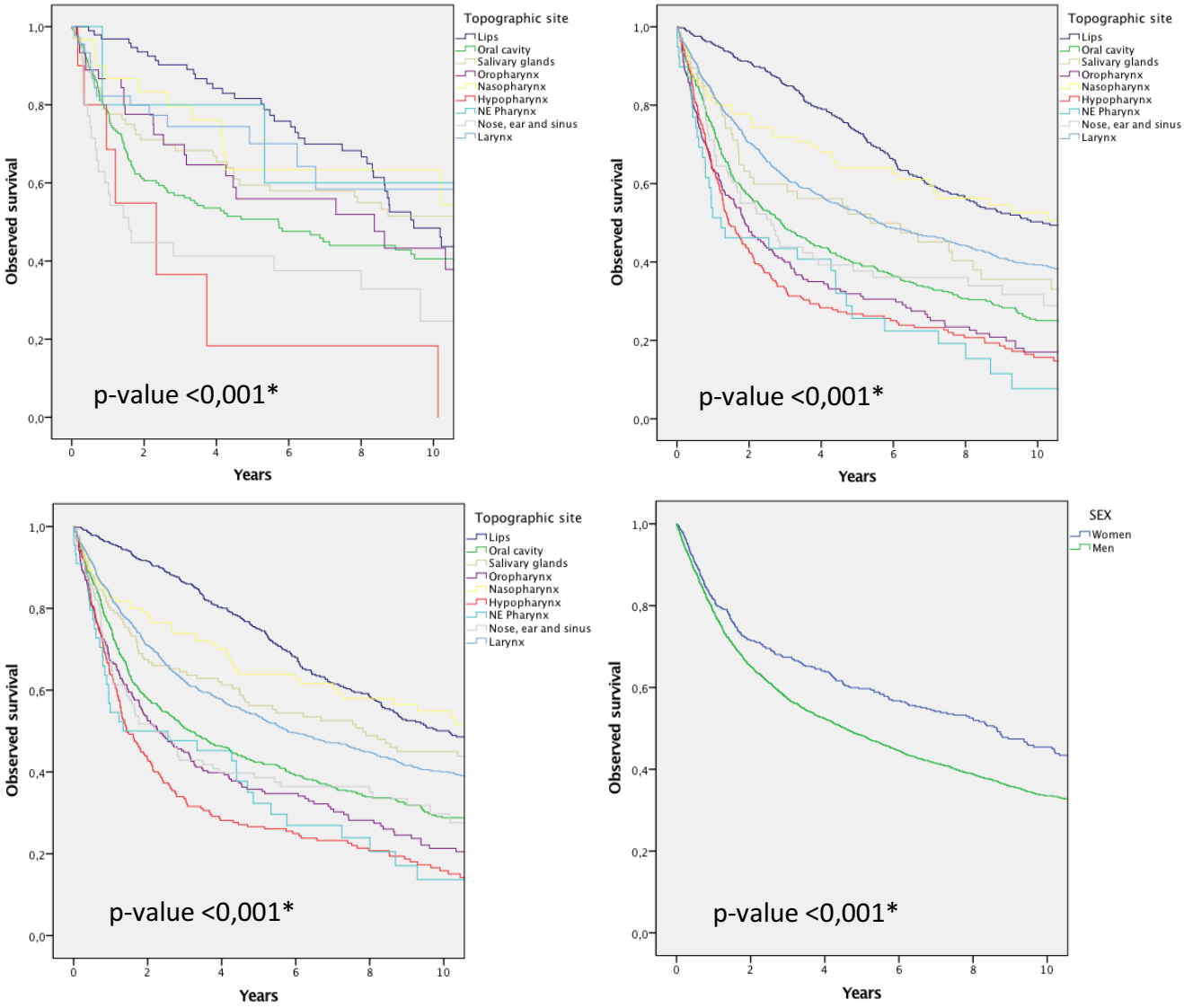
Table 7. Mean and Median (expressed in years) observed survival by sex and topographic site of HNC.

Topographic site	Mean OS (SD)			Median OS (SD)		
	Men	Women	Both sexes	Men	Women	Both sexes
Head and Neck Cancer	7.6 (0.16)	9.8 (0.41)	8.0 (0.15)	4.5 (0.25)	8.6 (0.84)	5.0 (0.25)
Lips	10.9 (0.41)	10.6 (0.69)	10.9 (0.37)	10.1 (1.0)	9.4 (0.76)	10.1 (0.88)
Oral cavity	6.2 (0.32)	8.3 (0.60)	6.7 (0.29)	2.8 (0.30)	5.7 (1.3)	3.1 (0.34)
Salivary glands	7.9 (1.0)	10.1 (0.95)	9.4 (0.75)	5.3 (2.0)	10.6 (2.3)	7.8 (1.4)
Oropharynx	4.7 (0.42)	8.6 (1.1)	5.4 (0.42)	1.8 (0.25)	8.3 (2.8)	2.2 (0.33)
Nasopharynx	11.2 (0.97)	12.4 (1.7)	11.5 (0.85)	12.9 (3.5)	19.6 (0.00)	12.9 (3.0)
Hypopharynx	4.2 (0.40)	3.2 (1.4)	4.2 (0.38)	1.4 (0.16)	2.3 (0.80)	1.4 (0.16)
NE Pharynx	3.7 (0.74)	13.6 (3.9)	5.2 (1.0)	1.2 (0.99)	-	1.3 (1.7)
Nose, ear and sinus	6.7 (0.94)	5.6 (1.1)	6.6 (0.80)	2.6 (0.49)	1.5 (0.43)	2.2 (0.52)
Larynx	8.5 (0.28)	13.3 (1.6)	8.6 (0.28)	5.6 (0.55)	-	5.7 (0.55)

SD, standard deviation; NE, not specified; OS, observed survival.

Mean and median (expressed in years) of the OS by sex and topographic site of HNC are shown in **table 7.** Initially, they may seem high but, we have to consider that cancer staging was not studied so if we specifically studied the HNC in advanced stage, the mean and median would be lower.

Figure 10 shows the OS graphics of HNC in general and divided by topographic sites. Statistical differences between curves were assessed using the log-rank test.



* Statistical differences between curves were assessed using the log-rank test.

Figure 10. In the upper left corner, we observe the OS of topographic site of HNC in women. In the upper right corner, we observe the OS of topographic site of HNC in men. In the lower left corner, we observe the OS of topographic site of HNC in both sex. In the lower right corner, we observe the OS of HNC in general divided by sex. All the OS of the graphic are part of patients of Girona province in the period of 1994 to 2013.

DISCUSSION

HNC is a very heterogeneous disease that comprises a large number of tumours with clinically and etiologically different characteristics. This study shows the epidemiological characteristics of HNC in general and divided in topographic sites of a retrospective cohort from Girona during 1994 to 2013 according to the age and the sex of the population.

Of all HNC, 96.6% were invasive, perhaps this is because most of the diagnoses are made in more advanced tumour stages(24). To be sure, we should deepen our study, analysing the cancer staging of each patient at the time of diagnosis.

HNC was more incident in men than women during the period of study (1994-2013). The large proportion of men compared to women may be due to a higher prevalence of male smokers in Catalonia and specifically in Girona(38). Regarding HNC incidence according to age, it was higher in men in all age groups. There were only minor differences in the age group of 0 to 24 years and perhaps they were not significant enough (we would need to compare them by sex using linear regression). These minor differences could be explained by the higher prevalence of female smokers in that age group(38).

There was a higher proportion of women in the group of patients with oral cavity than laryngeal cancer and the main histological subtype for them (and for both sexes and all age groups) was the SCN. These data are consistent with previously published findings(2,5). Related to the most common topographic site for both sexes, the larynx was superior to the oral cavity as opposed to several previous studies(2,24). Maybe it is due to the low number of female patients in this study compared to male patients (the larynx is the preferred HNC site in men as opposed to the oral cavity for women).

Regarding the incidence trend of HNC in Girona during the period of the study (1994-2013), it has decreased significantly in men and in the both sexes but not in women (APC was not statistically significant). Measure adopted to control the smoking habit may have influenced in this trend (see **annex 3**). In women may be not statistically significant due to the increasing incidence trend of tobacco's consumption(38).

The incidence trend of oropharyngeal cancer did not increase as we assumed it would (its rise was not statistically significant). On the other hand, it did not decrease, therefore we could say that the association of oropharyngeal tumours in Girona province with HPV should have had a role as a risk factor but it should not have been as strong as in USA(16,17,39).

Regarding observed survival, the nasopharyngeal cancer had the best result with 73.8% and 63.9% at 3 and 5 years respectively for both sexes. Most undifferentiated carcinomas were located in the nasopharynx, maybe that's why we got such a good survival. The improved concomitant chemo-radiotherapy has enabled the cure of the advanced stages of this tumour(37).

We recognize that our study is limited by the lack of information related to cancer staging (TNM), HPV confirmation or not, treatments made and other facts than they can influence survival. All these facts make it a distant vision but, with the advantage and the security to be a population-based study. In addition, due to the complexity in the classification of different tumours in their proper place in the classification of ICD-O(32), we found some possible errors related to that during the study. Examples include the classification of basal cell carcinomas on the lip and not in the lip skin (different topographic site according to the ICD-O (see **Annex 1**)) or the inclusion of some

lymphomas, which their primary origin was not the head and neck. All this could have caused minimal bias in our study.

CONCLUSIONS

1- HNC was more incident in men than women during the period of study (1994-2013) with a ASR_E of 50.0 and 8.9 respectively. Regarding HNC incidence according to age, it was higher in men in all age groups. There were only minor differences in the age group of 0 to 24 years.

2- The most frequent topographic site of HNC in Girona during the period of the study (1994-2013) was the larynx for men and the oral cavity for women with 35.24% and 36.2% respectively. Regarding the most frequent topographic site of HNC according to age, the larynx was the most frequent for men and the oral cavity for women in all age groups with an exception, the nasopharynx was the most frequent in the age group of 0 to 24 years for both sexes.

3- Squamous cell neoplasms were the most frequent histological type for both sexes and all age groups in the province of Girona during 1994 to 2013.

4- Incidence trend of HNC in Girona during the period of the study (1994-2013) has decreased significantly in men and in the both sexes but not in women (APC was not statistically significant).

5- Although the incidence trend of HNC in Girona has decreased, the trend of Oropharynx Cancer has not increased (APC was not statistically significant). A slight rise of incidence trend of Oropharynx Cancer can be observed for women

and for both sexes but these increases are not sufficient to support our hypothesis.

6- HNC survival in Girona during 1994 to 2013 is higher in women than in men in HNC in general and by topographic site of Head and Neck, except some topographic sites that there were not sufficient cases to calculate the observed survival in women.

WORK PLAN AND CHRONOGRAM

The sequence of activities at individual level or for the entire research team is described below following the scheme: Activity-Description-Days (D).

Preparation (PHASE 0)

Activity 1. Meetings with the Final Degree Project (FDP) advisor (Jordi Rubió Casadevall) to decide about the topic of the FDP (D1-D7).

Activity 2. Meeting with the director of Girona Cancer Registry (GCR) (Rafael Marcos Gragera) to decide which study variables to get (D8-D9).

Activity 3. Formation about: SPSS syntax, EPIDAT, JOINPOINT and observed survival analysis (D10-D13).

Data collect (PHASE 1)

Activity 4. Identification and anonymization of cases in the database of GCR for future analyses (D14-D15).

Activity 5. Debugging of the database to allow us to calculate the incidence and the survival (D16-D17).

Analyses and final evolution (PHASE 2)

Activity 6. Incidence analyses (D18-D28).

Activity 7. Incidence trend analyses of HNC and oropharynx cancer(D29-D33).

Activity 8. Observed survival analyses (D34-D44).

Activity 9. FDP writing (D26-D55).

Activity 10. Data validation (D56-D66).

Activity 11. Results dissemination, writing scientific papers and publication (D67-D247).

CHRONOGRAM

Days (September, 2016)	12	13	14	15	16	17	18	19	20	21	22	23	24
PHASE 0. Researchers: Jordi Rubió, Rafael Marcos, Òscar Moreno													
Meetings with the FDP advisor	■	■	■	■	■	■	■						
Meeting with the director of GCR								■	■				
Formation										■	■	■	■

Days (September, 2016)	25	26	27	28

PHASE 1. Researchers: Rafael Marcos, Jordi Rubió, Òscar Moreno									
Identification and anonymization	■	■							
Debugging database			■	■	■	■	■	■	■

Months (2016-2017)	September	October	November	December	January	February	March	April	May
PHASE 2. Researchers: Òscar Moreno									
Incidence analyses	■	■							
Incidence trend analyses		■							
Observed survival analyses		■							
FDP writing	■	■	■						
Data validation			■						
Result dissemination, writing scientific papers and publication			■	■	■	■	■	■	■

BUDGET

The budget of this final degree project has been **0€.** This is because the database that was used already had the necessary data. Computers and programmes used to realize the present study are used in daily practice.

The following budget is part of an optional project in order to deepen on the subject of study (knowing the TNM and the treatment of the tumours by reviewing patients' health records).

BUDGET	
	COSTS
Staff **-Meetings and formation: 500€x3 members** **-Prints**	1500€ 20€
	Subtotal: 1520€
Statistical Analysis **-Reviewing patients' health records: 3171 patients/each patient's health record 50€** **-Statistical team: 20€/h, a total of 10h for this final degree project**	158.550€ 200€
	Subtotal: 158.750€
Travel and subsistence costs **-National congress fee: 400€x2 people** **-National congress accommodation: 100€ each night, during 3 nights for 2 people** **-National congress traveling: 150€x2 people**	800€ 600€ 300€
	Subtotal: 1700€
Publication **-Paper revision** **-Paper publication (*Cancer epidemiology*)**	50€ 1500€
	Subtotal: 1550€
	TOTAL: 163.520€

ANNEX

ANNEX 1: HNC topographic and morphological codes used in this study according to ICD-O-3(32).

TOPOGRAPHY

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

C00.0 External upper lip
Vermilion border o 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 lower 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 labia, NOS

C00.6 Commissure of lip
Labial commissure

C00.8 Overlapping lesion of lip

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
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

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
Junction of hard and soft palate

C05.9 Palate, NOS
Roof of mouth

C06 OTHER AND USPECIFIED 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

C06.9 Mouth, NOS
Buccal cavity
Oral cavity
Oral mucosa
Minor salivary gland, NOS

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

C08.9 Major salivary gland, NOS
Salivary gland, NOS
(*excludes minor salivary glands, NOS C06.9)*

C09 TONSIL
C09.0 Tonsillar fossa

C09.1 Tonsillar pillar
Faucial pillar
Glossopalatine fold

C09.8 Overlapping lesion of tonsil

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
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

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

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
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 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

C30.1 Middle ear
- Inner ear
- Auditory tube
- Eustachian tube
- Mastoid antrum
- Tympanic cavity

C31 ACCESORY 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

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

C32.9 Larynx, NOS

MORPHOLOGY

801-804 Epithelial neoplasms, NOS

8020/3 Carcinoma, undifferentiated, NOS

805-808 Squamous cell neoplasms

8070/2 Squamous cell carcinoma in situ, NOS
- Epidermoid carcinoma in situ, NOS
- Intraepidermal carcinoma, NOS
- Intraepithelial squamous cell carcinoma

8070/3 Squamous cell carcinoma, NOS
Epidermoid carcinoma, NOS
Squamous carcinoma
Squamous cell epithelioma

8070/6 Squamous cell carcinoma, metastatic, NOS

8071/3 Squamous cell carcinoma, keratinizing, NOS
Epidermoid carcinoma, keratinizing
Squamous cell carcinoma, large cell, keratinizing

8072/3 Squamous cell carcinoma, large cell, nonkeratinizing, NOS
Epidermoid carcinoma, large cell, nonkeratinizing
Squamous cell carcinoma, nonkeratinizing, NOS

8073/3 Squamous cell carcinoma, small cell, nonkeratinizing
Epidermoid carcinoma, small cell, nonkeratinizing

8074/3 Squamous cell carcinoma, spindle cell
Epidermoid carcinoma, spindle cell
Squamous cell carcinoma, sarcomatoid

8075/3 Squamous cell carcinoma, adenoid
Squamous cell carcinoma, acantholytic
Squamous cell carcinoma, pseudoglandular

8076/2 Squamous cell carcinoma in situ with questionable stromal invasion
Epidermoid carcinoma in situ with questionable stromal invasion

8076/3 Squamous cell carcinoma, microinvasive

8081/2 Bowen disease (C44._)
Intraepidermal squamous cell carcinoma, Bowen type (C44._)

8082/3 Lymphoepithelial carcinoma
Lymphoepithelioma
Lymphoepithelioma-like carcinoma
Schmincke tumor (C11._)

8083/3 Basaloid squamous cell carcinoma

814-838 Adenomas and adenocarcinomas

8140/0 Adenoma, NOS

8140/1 Atypical adenoma
Bronchial adenoma, NOS (C34._)

8140/2 Adenocarcinoma in situ, NOS

8140/3 Adenocarcinoma, NOS

8140/6 Adenocarcinoma, metastatic, NOS

8144/3 Adenocarcinoma, intestinal type (C16._)
Carcinoma, intestinal type (C16._)

8200/0 Eccrine dermal cylindroma (C44._)
Cylindroma of skin (C44._)
Turban tumor (C44.4)

8200/3 Adenoid cystic carcinoma
Cylindroma, NOS *(except cylindroma of skin M-8200/0)*
Adenocarcinoma, cylindroid
Adenocystic carcinoma
Bronchial adenoma, cylindroid (C34._)

8240/1 Carcinoid tumor of uncertain malignant potential
Carcinoid tumor, argentaffin, NOS
Argentaffinoma, NOS

8240/3 Carcinoid tumor, NOS
Carcinoid, NOS
Bronchial adenoma, carcinoid (C34._)
Neuroendocrine carcinoma, low grade
Neuroendocrine carcinoma, well-differentiated
Neuroendocrine tumor, grade I
Typical carcinoid

8246/3 Neuroendocrine carcinoma, NOS

843 Mucoepidermoid neoplasms

8430/1 Mucoepidermoid tumor

8430/3 Mucoepidermoid carcinoma

855 Acinar cell neoplasms

8550/0 Acinar cell adenoma
Acinar adenoma
Acinic cell adenoma

8550/1 Acinar cell tumor
Acinic cell tumor

8550/3 Acinar cell carcinoma
Acinar adenocarcinoma
Acinar carcinoma
Acinic cell adenocarcinoma

ANNEX 2: TNM staging for organ and staging according to TNM classification. Classification of Malignant Tumours, 7th Edition (International Union Against Cancer (2010))(40)

1.Larynx	**T**	Supraglottis	T1: one area with normal vocal cord mobility T2: more than a supraglottic area or glottis extension with normal mobility T3: limited to the larynx with fixed vocal cord and/or invasion to the postcricoid region, medial wall of the piriform sinus or pre-epiglottic space T4: affectation to the cartilage or extra laryngeal tissues
		Glottis	T1: limited to vocal cords with normal mobility T1 a: only a vocal cord T1b: both vocal cords T2: affectation of supraglottis or subglottis and/or decreased mobility T3: limited to larynx with vocal cord fixed T4: as in the supraglottis
		Subglottis	T1: limited to subglottis T2: extension to glottis with a normal or decreased mobility T3, T4: as in the glottis, including the trachea
	N		N0: no lymph node involvement N1: one ipsilateral involved node ≤3 cm N2a: one ipsilateral involved node 3-6 cm N2b: multiple ipsilateral lymph nodes ≤6 cm N2c: bilateral or contralateral lymph nodes ≤6 cm N3: any lymph node >6 cm
	M	M0: absence of distant metastases M1: presence of distant metastases	
2.Oral cavity and Oropharynx	T	(Mobile tongue, mouth floor, gum, buccal mucosa, retromolar, soft palate, tonsils, pharyngeal walls and base of the tongue)	T1: <2 cm T2: 2-4 cm T3: >4 cm T4: any size with invasion of adjacent structures (bone, cartilage, soft parts)
	N/M		As the larynx
3.Hypopharynx	T	(Piriform sinus, postcricoid region and posterior wall)	T1: one area T2: more than an area T3: more than an area with fixation of the vocal cords T4: invasion of adjacent structures
4.Nasopharynx	N/M T		As the larynx T1: one area T2: more than an area T3: invades nasal cavity and/or oropharynx T4: affectation of the skull base or cranial nerves
	N/M		As the larynx

Table 8. TNM staging for organ.

Stage	T	N	M
0	T1	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1-T3	N1	M0
IV	T4	N0-N1	M0
	T1-T4	N2-N3	M0
	T1-T4	N0-N3	M1

Table 9. Staging according to TNM classification.

ANNEX 3: *Ley 42/2010, de 30 de diciembre, por la que se modifica la Ley 28/2005, de 26 de diciembre, de medidas sanitarias frente al tabaquismo y reguladora de la venta, el suministro, el consumo y la publicidad de los productos del tabaco.*

BOLETÍN OFICIAL DEL ESTADO
Núm. 318 Viernes 31 de diciembre de 2010 Sec. I. Pág. 109188

I. DISPOSICIONES GENERALES

JEFATURA DEL ESTADO

20138 *Ley 42/2010, de 30 de diciembre, por la que se modifica la Ley 28/2005, de 26 de diciembre, de medidas sanitarias frente al tabaquismo y reguladora de la venta, el suministro, el consumo y la publicidad de los productos del tabaco.*

JUAN CARLOS I
REY DE ESPAÑA

A todos los que la presente vieren y entendieren.

PREÁMBULO

La Ley 28/2005, de 26 de diciembre, de medidas sanitarias frente al tabaquismo y reguladora de la venta, el suministro, el consumo y la publicidad de los productos del tabaco, supuso un hito importante en la política de nuestro país en la lucha contra el tabaquismo, tanto en lo que se refiere a la prohibición de fumar en lugares públicos como a las medidas encaminadas a potenciar la deshabituación del tabaco y a tratar de erradicar a medio y largo plazo el hábito de fumar.

Transcurridos más de cuatro años de aplicación de la Ley, es patente, como se desprende de diversos estudios realizados al respecto, la necesidad de avanzar en la protección de la salud de los ciudadanos ampliando la prohibición de fumar en espacios públicos cerrados y colectivos, lo que, por otro lado, satisface las demandas de los ciudadanos, como corroboran encuestas oficiales recientemente realizadas.

Dos son los colectivos especialmente beneficiados de esta medida. Por un lado, el de menores, grupo especialmente sensible de población que está expuesto al humo del tabaco en los lugares públicos cerrados. Por otro lado, el de trabajadores del sector de la hostelería que se encuentra claramente desprotegido con respecto al resto de los trabajadores, al estar expuestos al humo de tabaco ajeno.

Por todo ello, y en la línea seguida en materia de prevención y control del tabaquismo por la Unión Europea, con una estrategia concreta de la Comisión Europea, cuyo objetivo es ampliar la prohibición de fumar en espacios cerrados en todos los Estados miembros en 2012, posición que corrobora la ratificación por España, en diciembre de 2004, del Convenio Marco para el Control del Tabaco de la OMS, esta ley, que modifica la Ley 28/2005, se encamina a avanzar en las limitaciones tendentes a aumentar los espacios libres de humo del tabaco.

Artículo único. *Modificación de la Ley 28/2005, de 26 de diciembre, de medidas sanitarias frente al tabaquismo y reguladora de la venta, el suministro, el consumo y la publicidad de los productos del tabaco.*

La Ley 28/2005, de 26 de diciembre, de medidas sanitarias frente al tabaquismo y reguladora de la venta, el suministro, el consumo y la publicidad de los productos del tabaco, queda modificada como sigue:

Uno. Se añaden una nueva letra e) al artículo 2, cuyo contenido pasa a ser el apartado 1 de este artículo, y un nuevo apartado 2, que quedan redactados del siguiente modo:

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«e) Espacios de uso público: lugares accesibles al público en general o lugares de uso colectivo, con independencia de su titularidad pública o privada. En cualquier caso, se consideran espacios de uso público los vehículos de transporte público o colectivo.

2. A efectos de esta Ley, en el ámbito de la hostelería, se entiende por espacio al aire libre todo espacio no cubierto o todo espacio que estando cubierto esté rodeado lateralmente por un máximo de dos paredes, muros o paramentos.»

Dos. Se añade un nuevo apartado 7 al artículo 3, que queda redactado del siguiente modo:

«7. El Gobierno, mediante Real Decreto, determinará los contenidos y componentes de los productos del tabaco, en especial los elementos adictivos, así como las condiciones de etiquetado que éstos deberán cumplir.»

Tres. Se modifica el primer párrafo del apartado b) del artículo 4, que queda redactado del siguiente modo:

«b) Ubicación: Las máquinas expendedoras de productos del tabaco sólo podrán ubicarse en el interior de quioscos de prensa situados en la vía pública y en locales cuya actividad principal sea la venta de prensa con acceso directo a la vía pública, en las tiendas de conveniencia previstas en el artículo 5.4 de la Ley 1/2004, de 21 de diciembre, de Horarios Comerciales, que estén ubicadas en estaciones de servicio, así como en aquellos locales a los que se refieren las letras k), t) y u) del artículo 7 en una localización que permita la vigilancia directa y permanente de su uso por parte del titular del local o de sus trabajadores.

En paralelo a la venta a través de máquinas expendedoras, se permitirá la venta manual de cigarros y cigarritos provistos de capa natural en dichos locales que cuenten con la autorización administrativa otorgada por el Comisionado para el Mercado de Tabaco.»

Cuatro. Se modifica la letra g) del artículo 5, que queda redactada del siguiente modo:

«g) En cualquier otro lugar, centro o establecimiento donde esté prohibido su consumo, así como en los espacios al aire libre señalados en el artículo 7, salvo lo previsto en la letra b) del artículo 4.»

Cinco. Se suprime la letra h) del artículo 5.

Seis. El artículo 6 queda redactado del siguiente modo:

«El consumo de productos del tabaco deberá hacerse exclusivamente en aquellos lugares o espacios en los que no esté prohibido.»

Siete. El artículo 7 queda redactado del siguiente modo:

«Artículo 7. *Prohibición de fumar.*

Se prohíbe fumar, además de en aquellos lugares o espacios definidos en la normativa de las Comunidades Autónomas, en:

a) Centros de trabajo públicos y privados, salvo en los espacios al aire libre.

b) Centros y dependencias de las Administraciones públicas y entidades de Derecho público.

c) Centros, servicios o establecimientos sanitarios, así como en los espacios al aire libre o cubiertos, comprendidos en sus recintos.

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d) Centros docentes y formativos, salvo en los espacios al aire libre de los centros universitarios y de los exclusivamente dedicados a la formación de adultos, siempre que no sean accesos inmediatos a los edificios o aceras circundantes.

e) Instalaciones deportivas y lugares donde se desarrollen espectáculos públicos, siempre que no sean al aire libre.

f) Zonas destinadas a la atención directa al público.

g) Centros comerciales, incluyendo grandes superficies y galerías, salvo en los espacios al aire libre.

h) Centros de atención social.

i) Centros de ocio o esparcimiento, salvo en los espacios al aire libre.

j) Centros culturales, salas de lectura, exposición, biblioteca, conferencias y museos.

k) Salas de fiesta, establecimientos de juego o de uso público en general, salvo en los espacios al aire libre.

l) Áreas o establecimientos donde se elaboren, transformen, preparen, degusten o vendan alimentos.

m) Ascensores y elevadores.

n) Cabinas telefónicas, recintos de los cajeros automáticos y otros espacios cerrados de uso público de reducido tamaño. Se entiende por espacio de uso público de reducido tamaño aquel que no ocupe una extensión superior a cinco metros cuadrados.

ñ) Estaciones de autobuses, salvo en los espacios que se encuentren al aire libre, vehículos o medios de transporte colectivo urbano e interurbano, vehículos de transporte de empresa, taxis, ambulancias, funiculares y teleféricos.

o) Todos los espacios del transporte suburbano (vagones, andenes, pasillos, escaleras, estaciones, etc.), salvo en los espacios que se encuentren por completo al aire libre.

p) Estaciones, puertos y medios de transporte ferroviario y marítimo, salvo en los espacios al aire libre.

q) Aeropuertos, salvo en los espacios que se encuentren al aire libre, aeronaves con origen y destino en territorio nacional y en todos los vuelos de compañías aéreas españolas, incluidos aquellos compartidos con vuelos de compañías extranjeras.

r) Estaciones de servicio y similares.

s) Cualquier otro lugar en el que, por mandato de esta Ley o de otra norma o por decisión de su titular, se prohíba fumar.

t) Hoteles, hostales y establecimientos análogos, salvo en los espacios al aire libre. No obstante, podrán habilitarse habitaciones fijas para fumadores, siempre que cumplan con los requisitos establecidos en el artículo 8.

u) Bares, restaurantes y demás establecimientos de restauración cerrados.

v) Salas de teatro, cine y otros espectáculos públicos que se realizan en espacios cerrados.

w) Recintos de los parques infantiles y áreas o zonas de juego para la infancia, entendiendo por tales los espacios al aire libre acotados que contengan equipamiento o acondicionamientos destinados específicamente para el juego y esparcimiento de menores.

x) En todos los demás espacios cerrados de uso público o colectivo.»

Ocho. El artículo 8 queda redactado del siguiente modo:

«En los lugares designados en la letra t) del artículo anterior se podrán reservar hasta un 30% de habitaciones fijas para huéspedes fumadores, siempre que se cumplan los siguientes requisitos:

a) Estar en áreas separadas del resto de habitaciones y con ventilación independiente o con otros dispositivos para la eliminación de humos.

b) Estar señalizadas con carteles permanentes.

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c) Que el cliente sea informado previamente del tipo de habitación que se pone a su disposición.

d) Que los trabajadores no puedan acceder a las mismas mientras se encuentra algún cliente en su interior, salvo casos de emergencia.»

Nueve. Se añade un nuevo apartado 3 al artículo 9, que queda redactado del siguiente modo:

«3. Se prohíbe en todos los medios de comunicación, incluidos los servicios de la sociedad de la información, la emisión de programas o de imágenes en los que los presentadores, colaboradores o invitados:

a) Aparezcan fumando.

b) Mencionen o muestren, directa o indirectamente, marcas, nombres comerciales, logotipos u otros signos identificativos o asociados a productos del tabaco.»

Diez. El artículo 12 queda redactado del siguiente modo:

«Artículo 12. *De los programas de deshabituación tabáquica.*

Las Administraciones públicas competentes promoverán el desarrollo de programas sanitarios para la deshabituación tabáquica en la red asistencial sanitaria, en especial en la atención primaria. Asimismo, se promoverán los programas de promoción del abandono del consumo de tabaco en instituciones docentes, centros sanitarios, centros de trabajo y entornos deportivos y de ocio. La creación de unidades de deshabituación tabáquica se potenciará y promoverá en el seno del Consejo Interterritorial del Sistema Nacional de Salud, que también definirá los grupos prioritarios que resulten más vulnerables.

El acceso a tratamientos de deshabituación tabáquica, cuya eficacia y coste-efectividad haya sido avalada por la evidencia científica, se potenciará y promoverá en el seno del Consejo Interterritorial del Sistema Nacional de Salud, valorando, en su caso, su incorporación a la cartera de servicios del Sistema Nacional de Salud.»

Once. El artículo 13 queda redactado del siguiente modo:

«Artículo 13. *Adopción de medidas.*

En la adopción de las medidas a que se refiere este capítulo, se atenderá, de manera particular, la perspectiva de género y las desigualdades sociales. Asimismo, las Administraciones públicas competentes promoverán las medidas necesarias para la protección de la salud y la educación de los menores, con el fin de prevenir y evitar el inicio en el consumo y de ayudar a estos en el abandono de la dependencia. Se introducirán contenidos orientados a la prevención y a la concienciación contra el tabaquismo en los planes formativos del profesorado. Se potenciará la puesta en marcha de programas de actuación en la atención pediátrica infantil, con información específica para los padres fumadores y campañas sobre los perjuicios que la exposición al humo provoca en los menores.»

Doce. Se modifica la letra a) del número 2 del artículo 19, que queda redactada del siguiente modo:

«a) Fumar en los lugares en que exista prohibición o fuera de las zonas habilitadas al efecto.»

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Trece. La letra d) del número 2 del artículo 19 queda redactada del siguiente modo:

«d) No informar en la entrada de los establecimientos de la prohibición de fumar o no cumplir el resto de obligaciones formales a que se refiere esta Ley.»

Catorce. Se suprime la letra e) del número 2 del artículo 19.

Quince. Se modifican las letras a) y b) del número 3 del artículo 19, que quedan redactadas del siguiente modo:

«a) Habilitar zonas para fumar en establecimientos y lugares donde no esté permitida su habilitación.

b) Permitir fumar en los lugares en los que existe prohibición de hacerlo.»

Dieciséis. El apartado 1 del artículo 20 queda redactado del siguiente modo:

«1. Las infracciones leves se sancionarán con multa de 30 a 600 euros, salvo la consistente en fumar en lugares prohibidos prevista en el artículo 19.2.a), que será sancionada con multa de hasta 30 euros si la conducta infractora se realiza de forma aislada; las graves, con multa desde 601 euros hasta 10.000 euros, y las muy graves, desde 10.001 euros hasta 600.000 euros.»

Diecisiete. En el apartado 2 del artículo 21 se suprime la referencia a la letra e) del artículo 19.2.

Dieciocho. Se modifica la disposición adicional primera, que queda redactada del siguiente modo:

«No obstante lo dispuesto en los artículos 3.1 y 5.g), en lo que se refiere a la venta a través de la red de expendedurías de tabaco y timbre y de máquinas expendedoras, se permite la venta manual de cigarros y cigarritos provistos de capa natural en los establecimientos a que se refiere la letra u) del artículo 7, que cuenten con autorización administrativa otorgada por el Comisionado para el Mercado de Tabacos.»

Diecinueve. Se suprime la disposición adicional segunda.

Veinte. Se modifica la disposición adicional tercera, que queda redactada del siguiente modo:

«Disposición adicional tercera. *Señalización de los centros o dependencias en los que existe prohibición de fumar y zonas habilitadas para fumar.*

En los centros o dependencias en los que existe prohibición legal de fumar deberán colocarse en su entrada, en lugar visible, carteles que anuncien la prohibición del consumo de tabaco y los lugares, en los que, en su caso, se encuentren las zonas habilitadas para fumar. Estos carteles estarán redactados en castellano y en la lengua cooficial con las exigencias requeridas por las normas autonómicas correspondientes.»

Veintiuno. Se modifica la disposición adicional cuarta, que queda redactada del siguiente modo:

«Lo dispuesto en esta Ley se entiende sin perjuicio de las peculiaridades del Régimen Económico Fiscal de Canarias, respecto de la libertad comercial de los productos del tabaco en los establecimientos comerciales situados en el archipiélago canario, sin que esta excepción suponga limitación en la aplicación de las demás prescripciones contenidas en esta Ley, en especial lo previsto en las letras a), b), c), d), e) y f) del artículo 5, en el artículo 9, y, en todo caso, las destinadas a la protección de menores.»

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Veintidós. Se modifica el segundo párrafo de la disposición adicional sexta, que queda redactado del siguiente modo:

«En los establecimientos penitenciarios se permite fumar a los internos en las zonas exteriores de sus edificios al aire libre, o en las salas cerradas habilitadas al efecto, que deberán estar debida y visiblemente señalizadas y contar con ventilación independiente o con otros dispositivos para la eliminación de humos.»

Veintitrés. Se modifica la disposición adicional séptima, que queda redactada del siguiente modo:

«Disposición adicional séptima. *Normativa sobre prevención de riesgos laborales.*

Lo establecido en esta Ley se entiende sin perjuicio de las demás limitaciones y prohibiciones al consumo de tabaco, contenidas en la normativa sobre prevención de riesgos laborales, cuya vigilancia y control corresponde a la Inspección de Trabajo y Seguridad Social.»

Veinticuatro. Se modifica la disposición adicional octava, que queda redactada del siguiente modo:

«Disposición adicional octava. *Centros o establecimientos psiquiátricos.*

En los establecimientos psiquiátricos de media y larga estancia se permite fumar a los pacientes en las zonas exteriores de sus edificios al aire libre, o en una sala cerrada habilitada al efecto, que habrá de estar debida y visiblemente señalizada y contar con ventilación independiente o con otros dispositivos para la eliminación de humos.»

Veinticinco. Se modifica la disposición adicional novena, que queda redactada del siguiente modo:

«Disposición adicional novena. *Clubes privados de fumadores.*

A los clubes privados de fumadores, legalmente constituidos como tales, no les será de aplicación lo dispuesto en esta Ley, relativo a la prohibición de fumar, publicidad, promoción y patrocinio, siempre que se realice en el interior de su sede social, mientras en las mismas haya presencia única y exclusivamente de personas socias.

A los efectos de esta Disposición, para ser considerado club privado de fumadores deberá tratarse de una entidad con personalidad jurídica, carecer de ánimo de lucro y no incluir entre sus actividades u objeto social la comercialización o compraventa de cualesquiera bienes o productos consumibles.

En ningún caso se permitirá la entrada de menores de edad a los clubes privados de fumadores.»

Veintiséis. Se añade una disposición adicional décima, que queda redactada del siguiente modo:

«Disposición adicional décima. *Centros residenciales de mayores o de personas con discapacidad.*

En los centros residenciales de mayores o de personas con discapacidad, se podrá habilitar una zona específica para fumadores, cuyo uso será exclusivo para residentes y deberá estar debida y visiblemente señalizada y contar con ventilación independiente o con otros dispositivos para la eliminación de humos, no pudiendo extenderse el permiso de fumar a las habitaciones ni al resto de las zonas comunes en dichos centros.»

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Veintisiete. Se añade una disposición adicional undécima, que queda redactada del siguiente modo:

«Disposición adicional undécima. *Informe a las Cortes Generales.*

El Ministerio de Sanidad y Política Social deberá remitir a las Cortes Generales, con carácter bienal y durante los cuatro años siguientes a la entrada en vigor de la Ley, un informe de evaluación del impacto de esta reforma sobre la salud pública.»

Veintiocho. Se modifica el apartado 2 de la disposición final primera, que queda redactado del siguiente modo:

«2. Corresponde a las Comunidades Autónomas, en su respectivo ámbito territorial, aprobar las normas de desarrollo y ejecución de esta Ley, incluidas las características y advertencias sanitarias correspondientes.»

Disposición final primera. *Título competencial.*

Esta Ley se dicta con carácter básico al amparo del artículo 149.1.1.ª, 16.ª, 18.ª y 27.ª de la Constitución.

Disposición final segunda. *Entrada en vigor.*

La presente Ley entrará en vigor el 2 de enero de 2011.

Por tanto,
Mando a todos los españoles, particulares y autoridades, que guarden y hagan guardar esta Ley.

Madrid, 30 de diciembre de 2010.

JUAN CARLOS R.

El Presidente del Gobierno,
JOSÉ LUIS RODRÍGUEZ ZAPATERO

cve: BOE-A-2010-20138

ANNEX 4: Summary descriptive of the epidemiology by sex and age groups, Girona 1994-2013

	0-24			25-49			50-74			75-+85		
	Men	**Women**	**Both**	**Men**	**Women**	**Both**	**Men**	**Women**	**Both**	**Men**	**Women**	**Both**
N (%)	8 (53.3)	7 (46.6)	15 (100)	388 (84.5)	71 (15.4)	459 (100)	1667 (87.0)	248 (12.9)	1915 (100)	535 (71.9)	209 (28.0)	744 (100)
Mean age (SD)	19.2 (3.3)	19 (6.3)	19.1 (4.7)	43.3 (5.2)	42.3 (6.5)	43.1 (5.4)	62.0 (6.9)	63.0 (7.4)	62.1 (7.0)	80.7 (4.7)	82.6 (5.1)	81.3 (4.9)
Median age (min-max)	19 (16-24)	21 (5-24)	21 (5-24)	45 (26-49)	44 (25-49)	45 (25-49)	62 (50-74)	63 (50-74)	62 (50-74)	80 (75-100)	82 (75-97)	80 (75-100)
CR	0.44	0.41	0.42	15.0	2.9	9.2	106.6	15.4	60.5	134.9	34.7	74.5
ASR_E	0.42	0.38	0.40	16.4	3.1	10.0	107.6	15.4	60.7	134.3	34.4	74.2
Histological subtypes N (%)												
SCN	3 (37.5)	1 (14.2)	4 (26.6)	312 (79.5)	45 (63.3)	357 (77.1)	1470 (87.3)	155 (62.2)	1625 (84.1)	425 (77.8)	134 (62.9)	559 (73.6)
AAA	0 (0.00)	0 (0.00)	0 (0.00)	3 (0.76)	6 (8.4)	9 (1.9)	19 (1.1)	13 (5.2)	32 (1.6)	9 (1.6)	3 (1.4)	12 (1.5)
UC	0 (0.00)	0 (0.00)	0 (0.00)	8 (2.0)	1 (1.4)	9 (1.9)	12 (0.71)	5 (2.0)	17 (0.88)	2 (0.36)	2 (0.93)	4 (0.52)
Others	5 (62.5)	6 (85.7)	11 (73.3)	69 (17.6)	19 (26.7)	88 (19.0)	181 (10.7)	76 (30.5)	257 (13.3)	110 (20.1)	74 (34.7)	184 (24.2)
Topographic site N (%)												
Lips	0 (0.00)	0 (0.00)	0 (0.00)	14 (3.5)	3 (4.2)	17 (3.6)	207 (12.3)	35 (14.0)	242 (12.5)	153 (28.0)	57 (26.7)	210 (27.6)
Oral cavity	2 (25)	2 (28.5)	4 (26.6)	104 (26.5)	25 (35.2)	129 (27.8)	360 (21.4)	88 (35.3)	448 (23.2)	105 (19.2)	80 (37.5)	185 (24.3)
Salivary glands	1 (12.5)	2 (28.5)	3 (20)	5 (1.2)	8 (11.2)	13 (2.8)	32 (1.9)	37 (14.8)	69 (3.5)	31 (5.6)	30 (14.0)	61 (8.0)
Oropharynx	0 (0.00)	0 (0.00)	0 (0.00)	50 (12.7)	6 (8.4)	56 (12.0)	160 (9.5)	28 (11.2)	188 (9.7)	37 (6.7)	13 (6.1)	50 (6.5)
Nasopharynx	3 (37.5)	2 (28.5)	5 (33.3)	41 (10.4)	10 (14.0)	51 (11.0)	43 (2.5)	15 (6.0)	58 (3.0)	6 (1.0)	4 (1.8)	10 (1.3)
Hypopharynx	0 (0.00)	0 (0.00)	0 (0.00)	33 (8.4)	3 (4.2)	36 (7.7)	172 (10.2)	5 (2.0)	177 (9.1)	25 (4.5)	2 (0.93)	27 (3.5)
NE pharynx	0 (0.00)	0 (0.00)	0 (0.00)	8 (2.0)	3 (4.2)	11 (2.3)	27 (1.6)	1 (0.40)	28 (1.4)	5 (0.91)	1 (0.46)	6 (0.79)
Nose, ear and sinus	2 (25)	1 (14.2)	3 (33.3)	18 (4.5)	4 (5.6)	22 (4.7)	42 (2.4)	11 (4.4)	53 (2.7)	15 (2.7)	19 (8.9)	34 (4.4)
Larynx	0 (0.00)	0 (0.00)	0 (0.00)	119 (30.3)	9 (12.6)	128 (27.6)	639 (37.9)	29 (11.6)	668 (34.5)	169 (30.9)	7 (3.2)	176 (23.1)
Behaviour N (%)*												
In situ	0 (0.00)	0 (0.00)	0 (0.00)	20 (5.1)	2 (2.8)	22 (4.7)	59 (3.5)	4 (1.6)	63 (3.2)	20 (3.6)	4 (1.8)	24 (3.1)
Invasive	8 (100)	7 (100)	15 (100)	372 (94.8)	69 (97.1)	441 (95.2)	1623 (96.4)	245 (98.3)	1868 (96.7)	526 (96.3)	209 (98.1)	735 (96.8)

N, number of cases; SD, standard deviation; CR, crude rate per 100,000 inhabitants/year; ASR_E, age-specific rate for the European standard population; SCN, squamous cell neoplasms; AAA, adenomas and adenocarcinomas; UC, undifferentiated carcinoma; NE, not specified.
*Only *in situ* and invasive were selected for this study.

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