FACULTY OF MEDICINE

FINAL DEGREE PROJECT

RISK OF SECOND MALIGNANT NEOPLASMS IN PATIENTS DIAGNOSED WITH HEAD AND NECK CANCER BETWEEN 1994-2014 IN GIRONA, SPAIN: A POPULATION-BASED STUDY

Oncology service

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ABBREVIATIONS

Abbreviation	Meaning
AIRTUM	Associazione Italiana Registri Tumori
ASR	Age Standardized Rate
BMI	Body Mass Index
CI	Confidence intervals
CR	Crude rate
EAR	Excess of absolute Risk
ENCR	European Network of Cancer Registries
EXP	Expected cases
FDP	Final Degree Project
GCR	Girona Cancer Registry
GDPR	General Data Protection Regulation
HNC	Head and neck cancer
HPV	Human Papillomavirus
HR	Hazard ratio
IACR	International Association of Cancer Registries
IARC	International Agency for Research of Cancer
ICD-O-3	International Classification of Diseases for Oncology, third edition
IDESCAT	Institut d'Estadistica de Catalunya
Nº	Number
OBS	Observed cases
OSCC	Oral Squamous Cell Carcinoma
SEER	Surveillance, epidemiology and end results
SIR	Standardized Incidence Ratio
SMN	Second malignant neoplasm
SPC	Second primary cancer
USA	United States of America
WHO	World Health Organization

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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. Risk factors implicated in this pathology are known, and many of them are associated with the risk to develop a second malignant neoplasm (SMN). This fact besides of the increase of 5-years surveillance of those patients, may promote the increment of risk of having a SMN.

Data/Methods: 2748 cases of HNC (lips, oral cavity, salivary glands, oropharyngeal, nasopharyngeal, hypopharyngeal, nose, ear and sinuses and laryngeal cancers) were identified in the Girona Cancer Registry (GCR) database during the period 1994-2014. 420 cases of SMN were identified in those patients (390 in men and 30 in women). These patients were analysed to evaluate which of them developed a second malignant neoplasm (SMN), where was the new cancer located and to estimate the risk of suffering a new neoplasm in comparison with general population by the calculation of the standardized incidence ratio (SIR) and the excessive absolute risk (EAR).

Results: Our study confirms the higher risk of a SMN in patients with a previous HNC, which was increased at all sublocations of the head and neck except primary tumours located at nasopharynx. Our male sample presented a SIR 3.25 (2.94 - 3.59) and an EAR 280.13 (240.97 - 322.38) while female population presented a SIR of 3.52 (2.37 - 5.02) and an EAR of 112.22 (61.12 -179.51). The risk of a SMN at any head and neck sites was incremented in patients with a previous cancer at oral cavity, salivary glands, oropharynx and larynx.

Conclusions: Our investigation verifies the higher risk of a SMN in patients with a previous HNC in our population. These results were similar after comparing our population with the Italian (AIRTUM), USA (SEER) and French (Jegú et al.), with a similar tendency.

Keywords: head and neck cancer; field cancerization; second malignant neoplasms; second cancers; standardized incidence ratio; excess of absolute risk; population-based cancer registry; epidemiology; tobacco; HPV.

CONTENTS

INTRODUCTION

1. Head and neck cancers. Second Malignant Neoplasms. What are them?

According to the Spanish Society of Medical Oncology, head and neck malignant tumours include those cancers situated at paranasal sinuses, nasopharynx, oropharynx (tonsil, soft palate, tongue base), hypopharynx, larynx, oral cavity, (oral mucosa, gum, hard palate, tongue and floor of mouth). Alcohol, tobacco, unhealthy diet and virus infections are factors implicated at tumour genesis [1]. [see figure 1].

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 those cells to migrate from the original site and spread to distant sites. If the spread is not controlled, cancer can result in death [2].

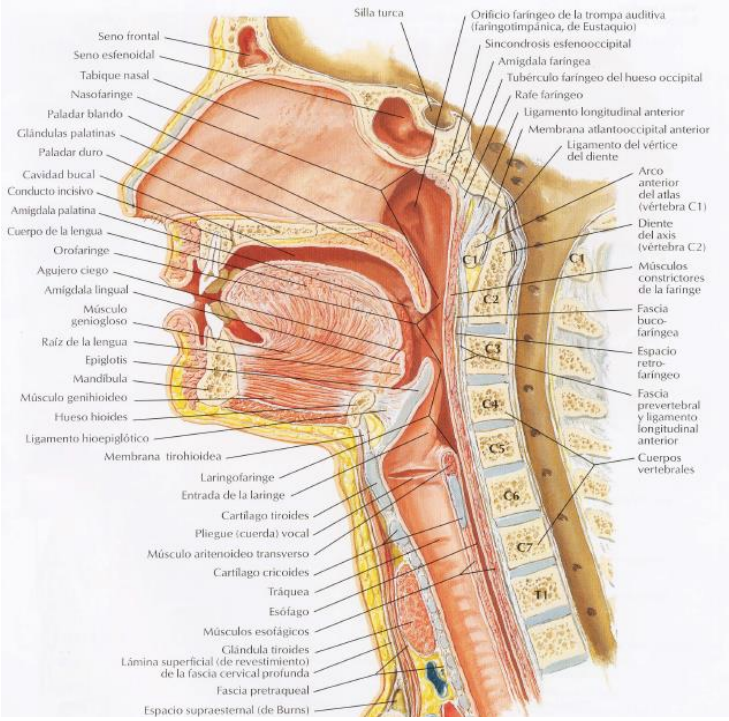

Figure 1. Picture showing a sagittal-section of the head. [4]

Second malignant neoplasms are defined as the appearance of a new malignant growth whose origin is biologically different from the first one [3].

Field cancerization is a relatively modern concept, devised by Slaughter and his collaborators, and updated by Dakubo et al in 2007, who defined it as “The process whereby cells in a particular tissue/organ are transformed, such that genetically altered but histologically normal appearing cells predate the development of neoplasia, irrespective of clonality” [5]. As it seems a healthy tissue, early detection of biological markers could be a helpful tool to prevent the develop of a malignant neoplasm.

Alterations of p53 expression have been reported to be an early event in the development of many carcinomas and its detection may be considered as a biomarker for these early stages of carcinogenesis [6]. An abnormal p53 expression is considered as a predictive of the transformation process of many types of epithelial dysplasia to cancer [7-8] especially OSCC, which is a tumour type accounting for more than 90% of head and neck malignancies [9].

Diagnosis of a new neoplasm at a cancer survivor is one of the worse sequelae that can befall [10]. Those second malignant neoplasms (SMN) represents up to 16% of cancers reported to the Nacional Cancer Institute of the United States of America (USA), with a clear rising prevalence [10]. In Spain, SMN conform up to 13% of new cancers diagnosed [1]. This situation is related to early detection and the development of more effective treatments against primary cancer, which, by increasing the 5-year relative survival, enhance the unwanted effects of the treatments, as well as the sequelae of cancer. Not only these factors are implicated at the growth of SMN, there some etiological, genetical and environmental factors that play a role in this process [Figure 1].

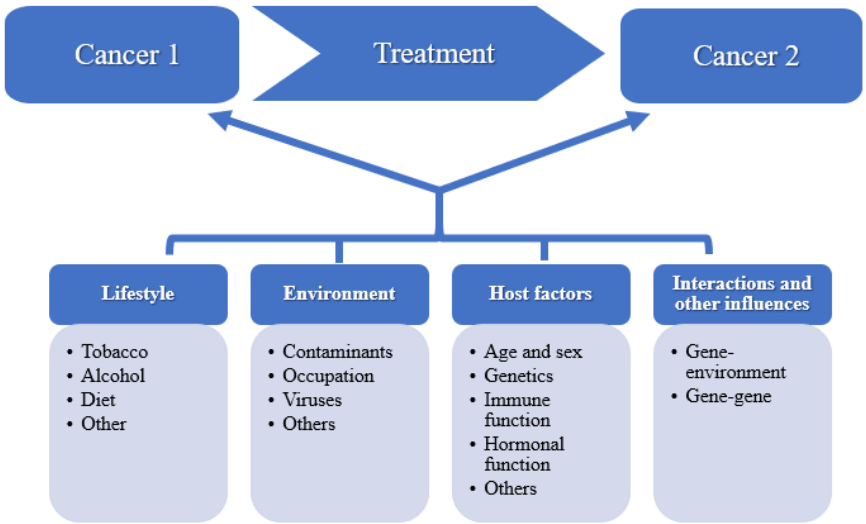

Figure 1. Risk factors in the develop of new neoplasms [10]

In any discussion of treatment-related second malignancies, it is of primary importance to remember that not all SMN are due to therapy. The occurrence of two primary malignancies in the same individual may reflect the interaction of numerous influences. Multiple primary cancers may result from host susceptibility (genetic predisposition or immunodeficiency), common carcinogenic influences, a clustering of risk factors, treatment for the first tumor, diagnostic surveillance, a chance event, or the interaction of these factors [10]. In view of the high prevalence of cancer in the general population and the increasing incidence of most cancers with age, it is important to exclude the role of chance in the development of second cancers.

To this end, comparison with cancer incidence statistics derived from the general population is crucial. If a second malignancy is demonstrated to occur in excess, the contributions of other risk factors need to be ruled out convincingly before the increased risk can be attributed to treatment. The temporal trend of excessive second cancer risk may provide an important initial clue to etiology.

2. Epidemiology of head and neck cancers.

HNCs are the seventh most common malignancy in the world with an estimated 827.659 new cancer cases diagnosed in 2018 (almost a 5% of all cancers) and an estimation of 10.244 new cases at Spain (see Table 1) (See figures 3,4) [11].

ICD-O	Cancer	Nº Cases estimated worldwide	CR	ASR	Nº Cases estimated at Spain	CR	ASR
C00-06	Lips and oral cavity	354.864	4.6	4.0	4.526	9.8	4.2
C07-08	Salivary Glands	52.799	0.7	0.6	635	1.4	0.6
C09-10	Oropharynx	92.887	1.2	1.1	1.165	2.5	1.4
C11	Nasopharynx	129.079	1.7	1.5	375	0.8	0.5
C12-13	Hypopharynx	80.608	1.1	0.9	854	1.8	1.0
C32	Larynx	177.422	2.3	2.0	2.689	5.8	2.9
Nº of estimated new cases		827.659			10.244		

Table 1. Estimated new cases of HNC worldwide and at Spain

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.

Age-standardized Rate (ASR): a fictitious summary rate statistically adjusted to remove the effect of a variable, ''age'' in this case, to permit unbiased comparison between groups having different compositions with respect to this variable.

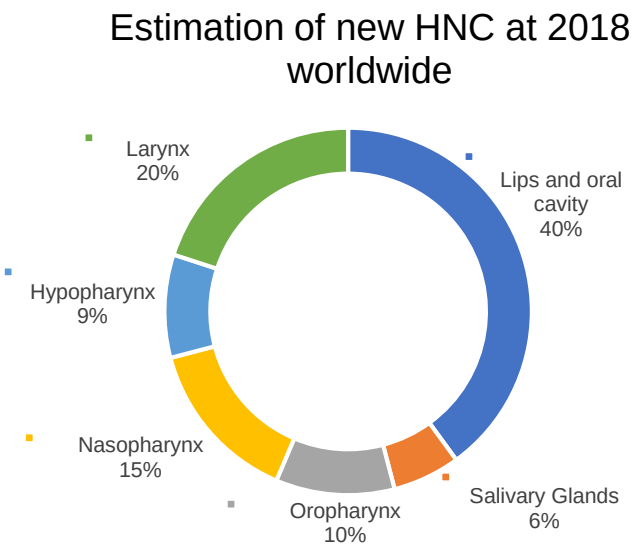

Figure 3. Estimation of new HNC at 2018 worldwide

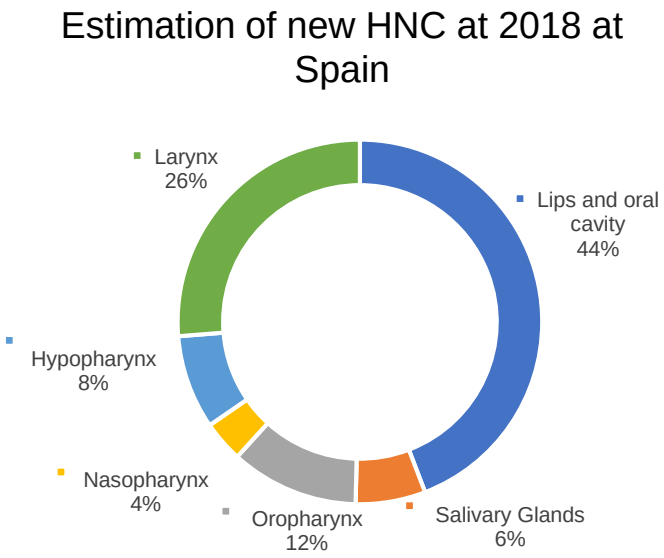

Figure 4. Estimation of new HNC at 2018 at Spain

These data show that the incidence of larynx and oral cavity cancer is higher in Spain, while the incidence of nasopharyngeal cancer is especially high worldwide.

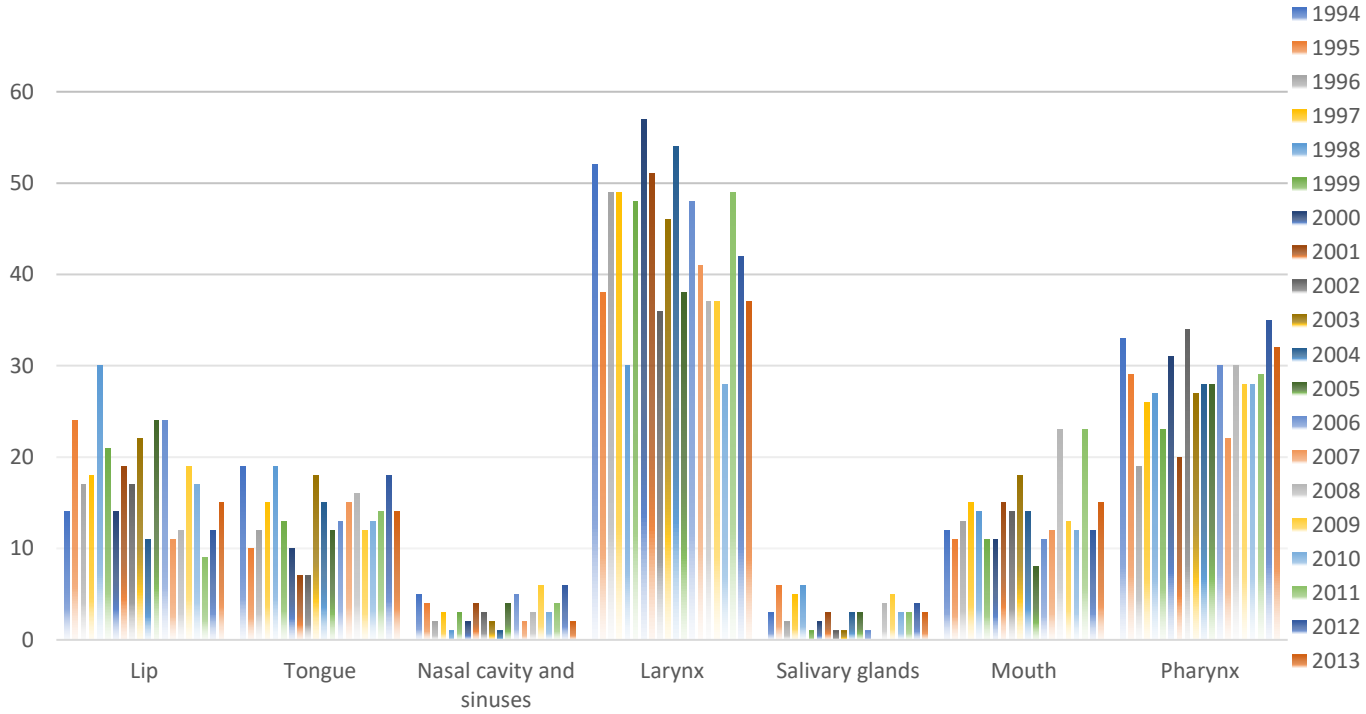

Figure 5. HNC diagnosed in Girona between 1994 and 2013 [12]

It calls our attention also that there are differences between HNC diagnosed at Girona between 1994 and 2014 (Figure 6, data extracted from the Girona Cancer Registry), where larynx and lip and oral cavity cancer had a similar incidence, and at Spain estimations, lips and oral cavity cancers present almost twice the incidence of larynx cancer.

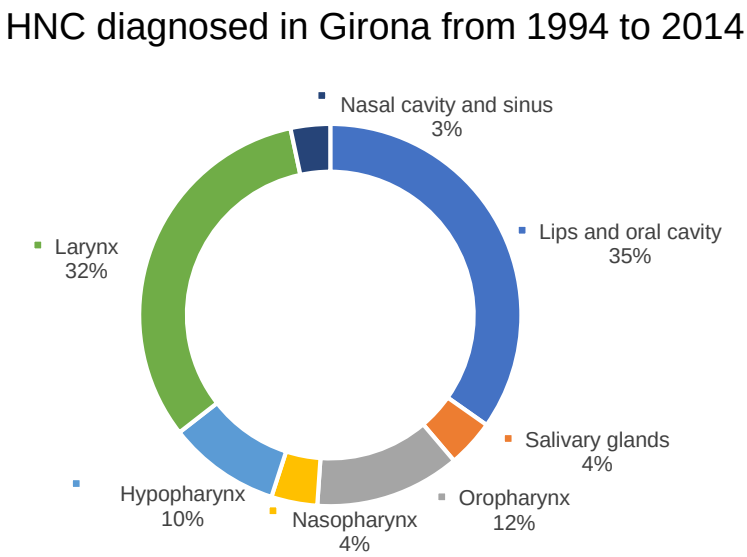

Figure 6. HNC diagnosed in Girona between 1994 and 2014

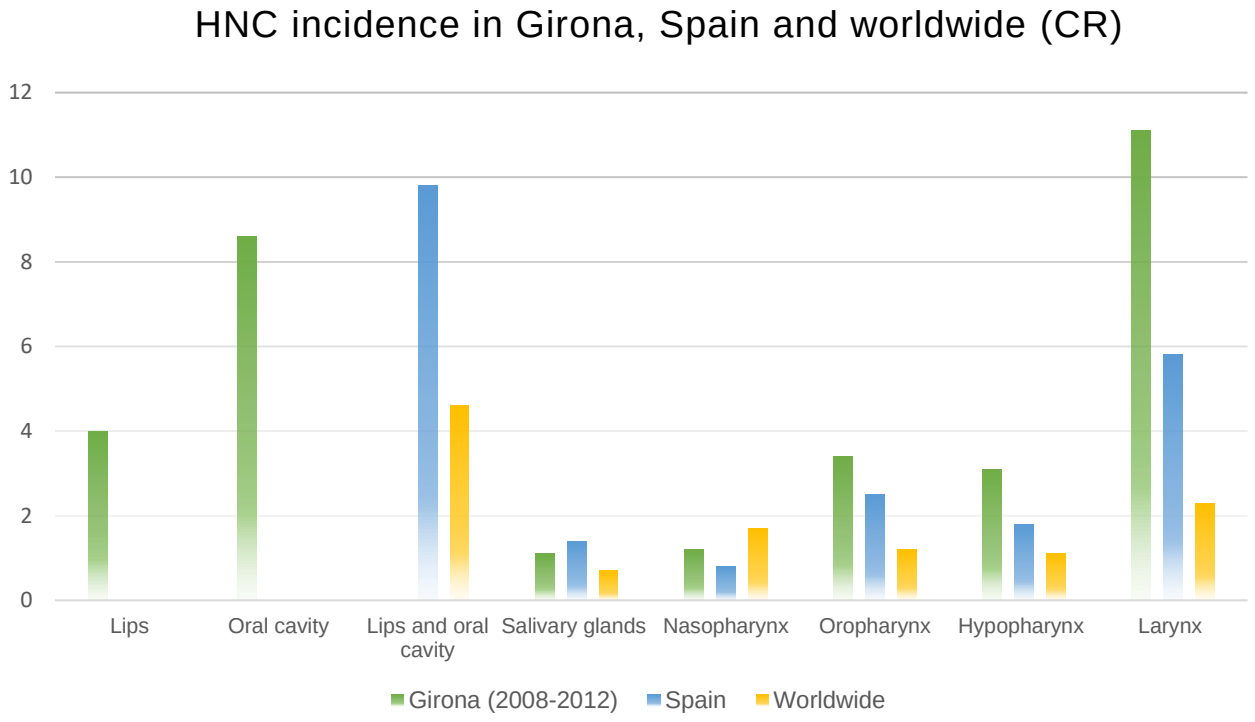

Figure 7. HNC incidence in Girona, Spain and worldwide (CR)

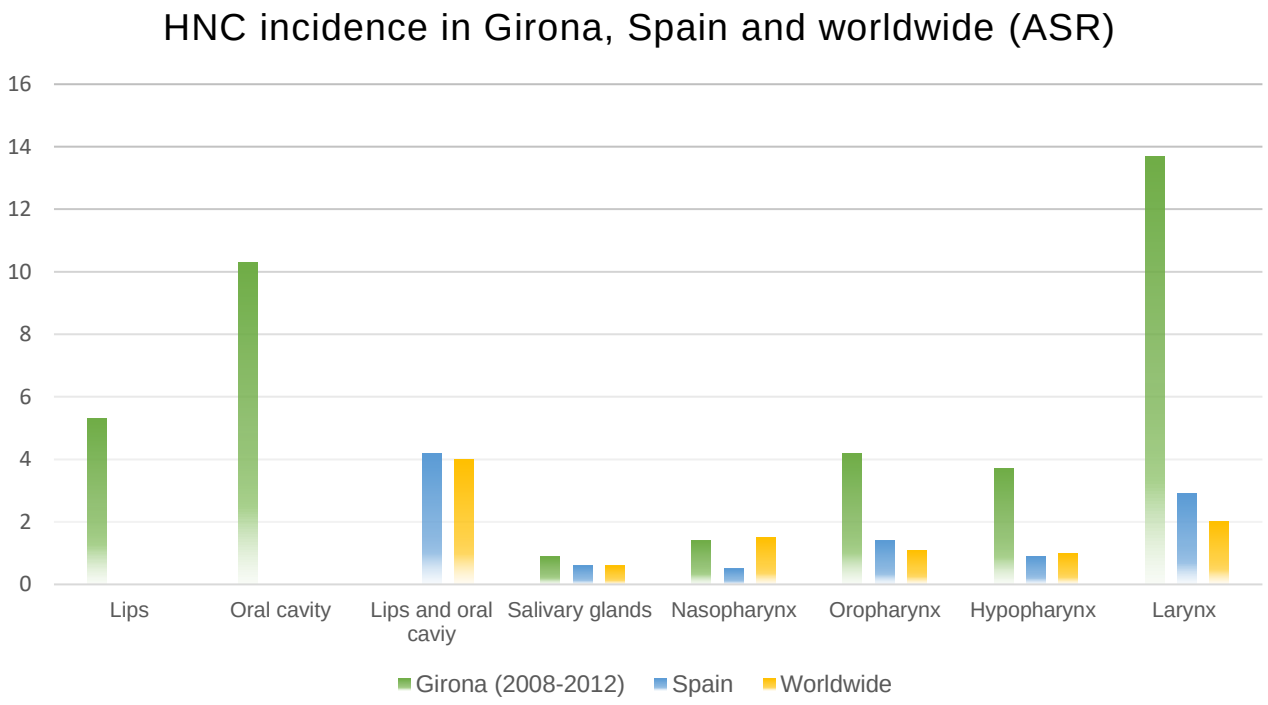

Figure 8. HNC incidence in Girona, Spain and worldwide (ASR)

With these figures we compare incidences between Girona, Spain and worldwide. We used the interval 2008-2012 because we think it is the most representative of our actual population. As we can see, incidences of almost all HNC are higher at Girona than at national population and worldwide population.

3. Risk factors to develop a second malignant neoplasm.

3.1. Environmental and lifestyle factors

3.1.1 Dietary and endocrine factors.

Diet and endocrine factors are established risk factors for determined cancers, where the genetics plays an important role. A Body Mass Index (BMI) over 25kg/m2 is considered a risk factor for oesophagus and thyroids cancer [13]. At the same time, studies at USA compared the mortality due to the cancer at patients with a BMI over 40kg/m2 (type 3 obesity or morbid obesity) and patients with a BMI less than 25kg/m2 (normal weight), where it was found a high relative risk at men [1.52 (95% CI, 1.13 to 2.05)] and women [1.62 (95% CI, 1.40 to 1.87)] with morbid obesity. This association was stronger in non-smokers patients [14].

3.1.2 Tobacco

Tobacco is one of the most important etiological factors at cancer growing, with well stablished associations with cancers located at superior aerodigestive tract (oral cavity, pharynx, larynx and oesophagus) [15]. It was found a positive correlation between smoking and P53 positivity in the benign and malignant oral mucosa tissue. The focally p53-positive mucosa in smokers samples might be an indication smoking induces early mucosal alterations in the development of OSCC [9].

In comparison with non-smokers, the consumption of 20 diary cigarettes is associated with an increase of risk of head and neck cancer (HR 4.45; 95% CI, 2.56 to 7.73) [16]. Accumulated incidence in the group of affected patients were in a range between 3% and 8%. This estimation was similar in those patients that have a primary cancer tobacco-related along all the cohort (HR 5.41; 95% CI, 5.23 to 5.61).

Risk of suffering a SMN is also determined by those patients that keep smoking after a primary cancer secondary to this substance. This is relatively common despite of the fact that it is a highly preventable risk factor. However, it is not clear if the elevated risk of appearing a new cancer due to tobacco exposure is due to the high prevalence of smokers between survivors of the first cancer or because of the increase of the susceptibility owing of the effects of smoking. This is because of the lack of available data.

3.1.3 Alcohol

Excessive alcohol use is related to cancers of the oral cavity, pharynx, larynx, oesophagus, colon, rectum, liver, and breast [15,17]. Synergistic effects of tobacco and alcohol exist for upper aerodigestive tract cancers [18]. In terms of absolute excess risk, tobacco- and alcohol related cancer sites are estimated to account for more than 35% of all subsequent malignancies [15].

3.1.4 Human Papillomavirus (HPV)

Human papillomavirus is a DNA virus that causes warts on acral parts which may be premalignant. It is usually identified by molecular biology techniques, that amplify the virus' DNA, allowing to identify the serotype.

Approximately the 33% of deaths due to squamous head and neck carcinomas are attributable to the development of a SMN at USA, being the second primary cancer (SPM) the first cause of long-term mortality in those patients [15,19,20].

In contrast to the trends in the other subsites, the excess risk of second cancers in patients with an index oropharyngeal SCC has declined dramatically since the early 1990s, with the risk of SPM having now declined to the lowest risk of any head and neck subsite [21]. Nonetheless, recently, HPV has been related with the majority of the oropharynx cancers reported, with a highly surveillance than non-squamous carcinomas non-HPV related.

This finding is consistent with the recent predominance of HPV associated oropharyngeal squamous cell carcinoma. Over the past 2 decades, the aetiology of oropharynx cancer has shifted from predominantly tobacco and alcohol–related to predominantly oncogenic HPV-related.

Patients with HPV-positive disease are more likely to lack systemic exposure to tobacco and alcohol and to be predominantly subjected to local exposure to an oncogenic virus with tropism for oropharyngeal epithelium. Now that the vast majority of oropharyngeal squamous cell cancers are viral in aetiology, the risk of SPM has declined to low levels. This explanation will be best validated in prospective or nested case-control studies. We believe that the significantly lower risk of SPM in modern HPV-related oropharyngeal SCC may be a major contributor to the demonstrated superior survival outcomes among patients with HPV-positive disease [22,23].

3.1.5 Interactions between factors

There are not many data referent to interactions between factors for the development of a SMN. In terms of excess of absolute risk (EAR), 35% of SMN appear on localizations susceptible to tobacco and/or alcohol localizations [24]. According to registered reports, it exists synergic relationships between lifestyle (like smoking) and treatments applied, increasing the risk of a SMN [10].

3.2 Treatment-related second malignant neoplasms

Modern treatment therapies have increased the survival of patients affected by cancer [4]. Over 60% of Spanish patients of cancer and 66.1% of USA patients have a survival relative rate above 5 years [10,25]. As result of the increased favourable prognosis, it is important to evaluate long-time effects of the treatments that have been used.

Studies carried out from 1970s to nowadays show that treatments against cancer are able to induce new primary malignancies [26]. This complication is considered one of the worst, due to its rise of morbidity and mortality.

It has been verified the increment of risk of developing a SMN after radiotherapy, chemotherapy or both modalities combined. However, it is difficult to evaluate the carcinogenic role of each therapeutic element, because treatments are frequently combined. It is necessary to use more epidemiological and statistical methods to quantify the excess risk and reveal the role of each therapeutic element. Without forgetting the results of previous studies of second neoplasms, we must remember that the problem of second neoplasms induced by treatment arises from the success of the treatment of the first cancer. Therefore, it is important to investigate the role played by the treatment as a potential risk of developing new neoplasms, since in this way, current therapies can be modified to reduce this risk while maintaining the levels of effectiveness.

3.2.1 Radiotherapy-related second malignant neoplasms

Radiotherapy plays a fundamental role at the curative treatment of cancer in adults. However, it is a risk factor to develop certain tumours. Secondary cancers derived from the use of radiotherapy are characterized by a latency above 5-10 years, and a tendency to appear inside or at the borders of the irradiated fields.

For certain SMN it has been established some risk-dose relationships, mainly in oesophageal, bladder cancer, breast, lung and thyroid cancer [27,28], as a possible exponential relationship at young ages at some cancers. That is why it is important to find new techniques that require less dose and a smaller field of irradiation [29].

3.2.2. Chemotherapy-related second malignant neoplasms

Relationship between chemotherapy and the develop of tumours with a variable latency is well stablished. This is the case that we find between alkylating agents and the risk of developing of acute non-lymphoblastic leukaemia [30], appearing usually during the first 10 years after treatment. Topoisomerase II inhibitors also present this leukemic potential, as well as platinum-based chemotherapy, but in those cases, the median latency is about 2-3 years, often affected by balanced translocations, with a better prognosis. [31,32,33].

3.3. Genetics-related SMN

3.3.1 Second Malignancies related to increased hereditary and familial risk

Identification of predisposing mutations of build-up of neoplasms, as a familiar history suggestive of a familiar cancer syndrome, allows to classify the cancer survivor as an above-average risk individual of suffer a SMN, becoming primordial screening strategies in those patients [10]. In those patients we have to keep in mind the probable aspect that can have the treatment applied at the first cancer as inductor of the second malignant neoplasm.

3.3.2 Genetic predisposition to therapy related SMNs

Response variability to the chemotherapy or radiotherapy is related with the genetic susceptibility. Late effects of treatment may be modified by moderate or low-penetrance genetic traits or by other gene – environment and gene – gene interactions. The importance of pharmacogenomics has been increasingly recognized, with estimates that genetics contributes 20-95% of the variability in cytotoxic drug disposition and effects [34].

Genetic polymorphisms in proteins involved in drug metabolism and transport are clinically relevant, as are variations in genes that encode receptors for target proteins of drugs and epidermal growth factor receptor tyrosine kinase inhibitors. Advances in molecular genetics and pharmacogenomics have linked polymorphisms in genes encoding selected drug-metabolizing enzymes, such as glutathione S -transferase, cytochrome P450s, and thiopurine methyltransferases, with the development of therapy-related cancer [24].

HYPOTHESES

1. Patients diagnosed with a head and neck carcinomas have a higher risk of suffering a SMN at other head and neck sites compared to the rest of the population.

2. Patients diagnosed with a head and neck carcinomas have a higher risk of suffering a SMN at distal anatomical sites compared to the rest of the population.

3. The risk of second malignant neoplasms are similar in other populations.

OBJECTIVES

1. To calculate the risk of SMN in patients diagnosed with a previous head and neck carcinoma at head and neck sites at Girona's population, with cases diagnosed between 1994 and 2014, by the calculation of standardized incidence ratio (SIR) and excess of absolute risk (EAR).

2. To determinate what distal areas are more susceptible to develop a second malignant neoplasm, by the calculation of standardized incidence ratio (SIR) and excess of absolute risk (EAR).

3. To compare our results with other studies made at other populations.

JUSTIFICATION

Head and neck cancers present several risk factors for their appearance that are well established. These factors are also implicated in the development of second malignant neoplasms, which are one of the worst sequelae that can suffer cancer patients. This fact, connected with the rise of 5-year surveillance at cancer patients all over the world, can allow that patients with a previous HNC develop a SMN, specially at head and neck locations due to the presence of risk factors at both pathologies. This risk will be calculated by statistical tools like the standardized incidence ratio (SIR) and the excess of absolute risk (EAR).

The impact of this new neoplasms is quite important. On one hand, at an emotional level for patients with a previous cancer, and on the other hand, at costs that sanitary system has to defray. According to this, if we found an increase of the risk, we could think about design new strategies that would allow to prevent this or new following-up programmes that permit us to give to the patients a better prognosis and economical savings for the sanitary system.

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

DATA AND METHODS

Study design

We present an observational, analytics, longitudinal and retrospective study performed in patients with a head and neck cancer diagnosed in the province of Girona between January 1st, 1994 to December 31st, 2014.

Population in study

This review is focused on patients with head and neck cancer diagnosed at any hospital in the province of Girona and recorded in the population-based Girona Cancer Registry from January 1st, 1994 to December 31st, 2014.

Inclusion criteria

Patients diagnosed with a head and neck cancer diagnosed between January 1st, 1994 to December 31st, 2014 and recorded in the population-based Girona Cancer Registry encoded by the International Classification of Diseases for Oncology, third edition (ICD-O-3.1) as: C00-C14; C30-C32 for topography (Table 2):

Lips	C00
Oral cavity	C01-02. Tongue C03. Gum C04. Floor of mouth C05. Palate C06. Other parts of the mouth
Salivary glands	C07. Parotid gland C08. Submaxillary and sublingual glands
Oropharynx	C09. Tonsil C10. Oropharynx
Nasopharynx	C11
Hypopharynx	C12. Pyriform sinus C13. Hypopharynx
Not specified pharynx	C14
Nose, ear and sinus	C30. Nasal cavity and ear C31. Sinus
Larynx	C32

Table 2. Codification for HNC cancers according to the ICD-O-3.1
This classification excludes sarcomas and skin, brain, bone, tooth and thyroid tumours

Data

Data was extracted from the Girona Cancer Registry (GCR). GCR is a population-based cancer registry located in the northeast of Catalonia and it covers 756.156 residents in Girona province, according to the census of 2014 provided by *L'Institut d'Estadistica de Catalunya (IDESCAT)*. The main objective of the GCR is to register new cases of cancer diagnosed each year in the residents of Girona and to obtain, thanks to this registry, epidemiological indicators of a cancer diagnosed in Girona, allowing the impact of cancer in population to be evaluated and controlled.

The number of patients that had a head and neck cancer (ICDO-10: C00-14, C30-32) in Girona between 1994 and 2014 was 2748 patients (353 lip cancers, 602 cancers at oral cavity, 111 at salivary glands, 107 at nasopharynx, 338 at oropharynx, 261 at hypopharynx, 92 at nasal cavities and sinus, and 884 at larynx).

In order to keep the registry updated, information sources are necessary, and are provided by:

- 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 the province. If microscopical verification is not possible, GCR will register the neoplasms diagnosed by exploratory techniques (clinical or surgical, imaging techniques or laboratory).
- Death certificates of some patients.

Due to the nature of this information, confidentiality agreement is necessary according to the *Ley orgánica 15/1999, 13 diciembre, de protección de datos de carácter personal*.

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 ICD-O-3, named before.

The cases registered as SMN were coded following the International Rules for Multiple Primary Cancer published by the International Agency for Research in Cancer (IARC), the International Association of Cancer Registries (IACR), World Health Organization (WHO) and European Network of Cancer Registries (ENCR) (see Annex 1).

Statistical analysis

Our population in study was composed by patients with a previous HNC diagnosed from 1994 to 2014 at Girona and find how many of them developed a SMN. The statistical tools to compare the risk used in this study were the excess of absolute risk (EAR) and the standardized incidence ratio (SIR). We assume that our population follows a Poisson distribution so, according to this, we build confidence intervals for SIR and EAR. For SIR, those results in which confidence intervals value ''1'' is not included, are considered statistically significative and for EAR, confidence intervals that do not include value ''0'', are considered statistically significative.

Excess of Absolute Risk

The EAR is the absolute risk of second cancer compared to the expected value. It is calculated using the following formula:

$$\frac{\textit{Observed Cases - Expected Cases}}{\textit{Person-years at risk}}$$

Where:

- **Observed Cases:** refers to the number of second cancers observed in the study population (actual measure).
- **Expected Cases:** refers to the number of second cancers that would have been observed in the study population if it had experienced the levels of incidence of the general population (without prior diagnosis of cancer) of the same age and sex. It is a fictional (theoretical) measure of comparison.
- **Person-years at risk:** refers to the total number of person-years during which the study population was followed (i.e., was at risk of developing a second cancer). The EAR is expressed per 1,000 person-years.

The interpretation is:

- **Value above 0:** The absolute number of excess (second) cancers observed in the study population compared to the general population per 1,000 person-years.
- **Value equal to 0:** The absolute number of (second) cancers observed in the study population is equal to the number of (first) cancers observed in the general population.
- **Value below 0:** The absolute number of fewer (second) cancers observed in the study population compared to the general population per 1,000 person-years.

Standardized Incidence Ratio

The SIR is the Standardized Incidence Ratio; it is calculated as:

$$\frac{\textit{Observed Cases}}{\textit{Expected Cases}}$$

The interpretation is:

- **An SIR value higher than 1** means that the risk of developing a (second) tumour in the cancer population is higher than the risk of developing a (first) tumour in the general population.
- **An SIR value equal to 1** means that the risk of developing a (second) tumour in the cancer population is equal to the risk of developing a (first) tumour in the general population.
- **Finally, an SIR value lower than 1** means that the risk of developing a (second) tumour in the cancer population is lower than the risk of developing a (first) tumour in the general population.

ETHICAL ASPECTS

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the Code of Medical Deontology.

Due to the nature of this information, confidentiality agreement is necessary according to:

- *Ley orgánica 15/1999, 13 diciembre, de protección de datos de carácter personal.*
- *Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016.* Regulation on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing *Directive 95/46/EC*.
- *General Data Protection Regulation (GDPR)* published on May 4th, 2016 in the Official Journal of the European Union.

RESULTS

2.748 cases of HNC were identified in the GCR database during the period 1994-2014. Of these 2.748, 353 were lip cancer, 602 cancers were located at oral cavity, 111 at salivary glands, 107 at nasopharynx, 338 at oropharynx, 261 at hypopharynx, 92 at nasal cavities and sinus and 884 at the larynx.

420 cases of SMN were identified in those patients (390 in men and 30 in women). The tables included in Annex 2 contain the number of SMN diagnosed after each cancer, and the calculus of the risk of a SMN depending on the previous cancer. The statistically significant results of SIR and EAR are marked with an asterisk.

Patients with a previous lip cancer have a higher risk of SMN broadly, independent of sex. It seems that male patients are more likely to have a SMN at oropharynx, oesophagus, colon, rectum and anus, lung, prostate, urinary tract and non-Hodgkin Lymphoma, while for female patients we have no significant results at any specific location.

The group with a previous oral cavity cancer also has an incremented risk of a SMN. Male patients are susceptible to suffer a SMN at head and neck locations concretely at oral cavity, oropharynx, hypopharynx and larynx. Also, at oesophagus, lungs, and urinary tract. For female we have no significant data at any location.

Men with a previous salivary gland cancer have a higher risk of a SMN in general, also they have an incremented risk at lip, head and neck and lung, while women have more chances to have a SMN at the breast.

Women with a previous nasopharynx cancer have an incremented risk of a SMN at mammary gland. For men we did not find any significant relationship.

The risk of a SMN is incremented at men with a previous oropharynx cancer, especially at oral cavity, larynx, head and neck, oesophagus and lung. For women we had no significant data.

Men with a previous hypopharynx cancer are more likely to have a SMN at oesophagus, colon and lung, presenting an incremented risk at all. However, women only present it at oesophagus.

Male patients with a previous nasal cavity or sinus cancer have a highly increased risk of SMN, especially in the lung. For female patients we have no significant data.

At men with a previous larynx cancer, there were significant results for a higher risk of SMN broadly, at head and neck locations (especially at oral cavity, oropharynx and hypopharynx), colon, rectum and anus, lung, prostate, urinary tract (urinary bladder), thyroid and non-Hodgkin lymphoma. For women the risk of developing a SMN at any other site, is not significant.

All the set of patients with a previous head and neck presented an incremented risk of a second neoplasm. This evidence was found in both sexes for head and neck, oesophagus, colon, rectum, anus, and thyroid secondary carcinomas. In male patients this higher risk was also present for oral cavity, oropharynx, hypopharynx, larynx, lung, urinary tract (urinary bladder), prostate cancers and non-Hodgkin lymphoma, while female patients presented this at mammary gland and thyroid.

DISCUSSION

HNC is a very heterogeneous disease that comprises many tumours with clinically and etiologically different characteristics. However, tumours with a known risk factor of developing it, present a higher risk of SMN in locations that are susceptible to the same risk factor. This study shows the incremented risk of SMN in patients with a previous HNC, in general and divided into topographic sites, of a retrospective cohort from Girona during 1994 to 2014 according to the sex of the population and the location of the first tumour. We compared our population with United States of America (USA) (Surveillance, epidemiology and end results, SEER) [24], Italy (Associazione Italiana Registri Tumori, AIRTUM) [35] and France (Jegú et al) [36] populations. We chose these studies because they are the most recent ones.

LIP PRIMARY CANCER																				
	MEN												WOMEN							
	GCR				JEGU				SEER				GCR				SEER			
SECOND TUMORAL TYPE	OBS	EXP	SIR (CI 95%)	EAR (CI 95%)	OBS	EXP	SIR	EAR (CI 95%)	OBS	EXP	SIR	EAR	OBS	EXP	SIR (CI 95%)	EAR (CI 95%)	OBS	EXP	SIR	EAR
Lip	0	0.16	0.00 (0.00 - 23.87)	-0.80 (-0.80 - 18.27)	No data				69	8.73	7.90*	9.30	0	0.00	0.00 (0.00 - 999.99)	-0.02 (-0.02 - 131.89)	6	0.19	32.36 *	6.58
Oral cavity	0	0.09	0.00 (0.00 - 42.47)	-0.45 (-0.45 - 18.61)	No data				37	9.37	3.95*	4.26	1	0.00	1559.7 6 (0.62 - 999.99)	33.62 (-0.01 - 192.84)	6	0.78	7.69*	5.91
Salivary glandules	0	0.03	0.00 (0.00 - 136.22)	-0.14 (-0.14 - 18.92)	No data				18	3.64	4.94*	2.22	0	0.00	0.00 (0.00 - 999.99)	-0.01 (-0.01 - 131.89)	1	0.26	3.90	0.84
Oropharynx	2	0.05	37.80 (3.56 - 139.02) *	9.47 (0.66 - 35.51) *	No data				0	1.08	0.00	-0.17	0	0.00	-0.01 (0.00 - 999.99)	-0.01 (-0.01 - 131.90)	0	0.05	0.00	-0.06
Nasopharynx	0	0.01	0.00 (0.00 - 474.23)	-0.04 (-0.04 - 19.02)	No data				1	1.20	0.83	-0.03	0	0.00	0.00 (0.00 - 999.99)	0.00 (0.00 - 131.90)	0	0.07	0.00	-0.08
Hypopharynx	0	0.04	0.00 (0.00 - 106.41)	-0.18 (-0.18 - 18.88)	No data				4	4.18	0.96	-0.03	0	0.00	0.00 (0.00 - 999.99)	0.00 (0.00 - 131.90)	0	0.13	0.00	-0.14
Nasal cavities and sinus	0	0.02	0.00 (0.00 - 239.28)	-0.08 (-0.08 - 18.98)	No data				5	2.11	2.37	0.45	0	0.00	0.00 (0.00 - 999.99)	-0.01 (-0.01 - 131.89)	1	0.18	5.71	0.93
Larynx	1	0.21	4.82 (0.00 - 27.63)	3.85 (-1.01 - 26.87)	No data				38	20.25	1.88*	2.74	0	0.00	0.00 (0.00 - 999.99)	0.00 (0.00 - 131.90)	1	0.45	2.24	0.63
Head and neck	3	0.61	4.94 (0.93 - 14.63)	11.64 (-0.20 - 40.23)	No data				No data				1	0.00	517.93 (0.21 - 999.99)	33.58 (-0.05 - 192.80)	No data			
Oesophagus	2	0.15	13.12 (1.24 - 48.26) *	8.98 (0.18 - 35.03) *	7	1.79	3.91*	12.8 (2.5 - 31.0)	21	17.24	1.22	0.58	0	0.00	0.00 (0.00 - 999.99)	-0.02 (-0.02 - 131.89)	0	0.82	0 .00	-0.93
Colon	3	1.71	1.76 (0.33-5.20)	6.28 (-5.55-34.88)	No data				134	139.92	0.96	-0.91	0	0.02	0.00 (0.00 – 166.52)	-0.79 (-0.79-131.11)	16	16.88	0.95	-1.00
Rectum	4	0.67	5.98 (1.56 - 15.47) *	16.20 (1.81 - 47.04) *	No data				56	56.79	0.99	-0.12	0	0.01	0.00 (0.00 - 406.29)	-0.32 (-0.32-131.58)	8	4.87	1.64	3.54
Colon, rectum and anus	7	2.38	2.95 (1.17 - 6.10) *	22.48 (1.94 - 58.97) *	No data				No data				0	0.03	0.03 (0.00 - 118.11)	-1.12 (-1.12 - 130.79)	No data			
Lung	18	2.03	8.86 (5.24 - 14.03) *	77.65 (41.88 - 128.72) *	27	9.52	2.84*	42.8 (20.3 - 72.9)	384	246.30	1.56*	21.25	0	0.01	0.00 (0.00 - 743.47)	-0.18 (-0.18 - 131.73)	25	15.22	1.64*	11.06
Prostate	9	3.64	2.47 (1.12 - 4.71) *	26.05 (2.13 - 65.73) *	No data				401	441.87	0.91	-6.31								
Mammary gland													1	0.03	30.25 (0.01-173.39)	32.53 (-1.10-191.75)	40	34.03	1.18	6.75
Urinary bladder	6	1.82	3.30 (1.19 - 7.22) *	20.32 (1.65 - 55.07) *	No data				115	110.19	1.04	0.74	0	0.01	0.00 (0.00 - 554.96)	-0.24 (-0.24 - 131.67)	5	4.04	1.24	1.09
Urinary tract	6	1.90	3.16 (1.14 - 6.91) *	19.93 (1.25 - 54.68) *	No data				151	148.15	1.02	0.44	0	0.01	0.00 (0.00 - 474.99)	-0.28 (-0.28 - 131.63)	6	6.53	0.92	-0.60
Non-Hodgkin lymphoma	3	0.32	9.50 (1.79 - 28.11) *	13.05 (1.21 - 41.65) *	No data				3	4.12	0.73	-0.17	0	0.00	0.00 (0.00 - 854.21)	-0.15 (-0.15 - 131.75)	2	0.90	2.22	1.24
Another	5	1.35	3.70 (1.17 - 8.69) *	17.73 (1.09 - 50.61) *	No data				11	3.17	3.47*	1.21	0	0.03	0.00 (0.00 - 153.58)	-0.86 (-0.86 - 131.04)	5	4.97	1.01	0.03
All (excluding no melanoma skin tumours)	58	15.42	3.76 (2.86 - 4.86) *	207.05 (139.1 3 - 289.79) *	No data				1,662	1,435.5 4	1.16*	34.95	4	0.17	23.37 (6.08 - 60.44) *	128.82 (29.25 - 342.24) *	152	126.8 8	1.20*	28.42

Table 3. Risk of SMN in patients diagnosed of previous lip cancer

Lip cancer has a strong relation with tobacco consumption [1]. According to this, it seems reasonable that locations that are susceptible to this factor, present a higher risk of a SMN (Table 3). This fact, together with the presence of other risk factors to develop a SMN, could explain why the risk is significantly increased in the lung in populations as different as Girona, France and USA. Maybe because of our sample was not too numerous, results can differ, but the risk is incremented in other locations tobacco-related, as we can check at larynx, prostate, urinary bladder and urinary tract. It is interesting that the risk of a SMN in oesophagus in men, where is well known the effects of tobacco, it is incremented among European countries but not at the USA.

ORAL CAVITY PRIMARY CANCER																
	MEN							WOMEN								
	GIRONA CANCER REGISTRY				AIRTUM			GIRONA CANCER REGISTRY				AIRTUM		
SECOND TUMORAL TYPE	OBS	EXP	SIR (CI 95%)	EAR (CI 95%)	OBS	SIR	EAR	OBS	EXP	SIR (CI 95%)	EAR (CI 95%)	OBS	SIR	EAR
Lip	0	0.24	0.00 (0.00 - 16.52)	-1.56 (-1.56 - 24.26)	No data			0	0.01	0.00 (0.00 - 321.61)	-0.17 (-0.17 - 54.94)	No data		
Oral cavity	3	0.15	20.31 (3.83 - 60.13) *	18.79 (2.75 - 57.53) *	47	6.69	1.10	0	0.03	0.00 (0.00 - 155.93)	-0.35 (-0.35 - 54.75)	33	23.41	1.75
Salivary gland	0	0.04	0.00 (0.00 - 105.01)	-0.25 (-0.25 - 25.58)	No data			0	0.01	0.00 (0.00 - 453.65)	-0.12 (-0.12 - 54.99)	No data		
Pharynx – Oropharynx	4	0.10	40.59 (10.56 - 104.96) *	25.70 (6.20 - 67.49) *	78	11.80	1.97	0	0.00	0.00 (0.00 - 924.70)	-0.06 (-0.06 - 55.05)	11	19.80	0.58
Pharynx – Nasopharynx	0	0.01	0.00 (0.00 - 275.87)	-0.09 (-0.09 - 25.73)				0	0.00	0.00 (0.00 - 999.99)	-0.02 (-0.02 - 55.09)			
Pharynx – Hypopharynx	2	0.07	28.21 (2.66 - 103.73) *	12.71 (0.77 - 47.99) *				0	0.00	0.00 (0.00 - 999.99)	-0.01 (-0.01 - 55.10)			
Nasal cavities and sinus	0	0.03	0.00 (0.00 - 155.07)	-0.17 (-0.17 - 25.66)	No data			0	0.00	0.00 (0.00 - 935.60)	-0.06 (-0.06 - 55.05)	No data		
Larynx	6	0.33	18.35 (6.60 - 40.20) *	37.37 (12.07 - 84.45) *	136	8.52	3.30	1	0.00	554.18 (0.22 - 999.99)	14.03 (-0.02 - 80.55)	14	22.72	0.74
Head and neck	15	0.96	15.65 (8.73 - 25.88) *	92.50 (48.82 - 157.07) *	261	8.82	6.37	1	0.06	17.23 (0.01 - 98.76)	13.24 (-0.81 - 79.76)	58	22.47	3.06
Oesophagus	5	0.24	20.99 (6.62 - 49.37) *	31.37 (8.82 - 75.91) *	146	20.10	3.82	1	0.01	74.90 (0.03 - 429.33)	13.87 (-0.18 - 80.39)	29	28.53	1.55
Lung	29	3.09	9.40 (6.29 - 13.52) *	170.72 (107.51 - 254.36) *	423	3.76	8.55	1	0.10	10.14 (0.00 - 58.14)	12.67 (-1.38 - 79.19)	66	5.21	2.95
Prostate	6	5.28	1.14 (0.41 – 2.49)	4.76 (-20.54 – 51.83)	103	0.87	-0.43							
Mammary gland								2	0.62	3.24 (0.31 – 11.93)	19.45 (-6.02 – 94.72)	70	1.39	1.08
Urinary tract	7	2.73	2.57 (1.02 - 5.32) *	28.14 (0.31 - 77.58) *	109	1.59	1.11	0	0.15	0.00 (0.00 - 26.95)	-2.05 (-2.05 - 53.06)	4	0.52	-0.21
All (excluding no melanoma skin tumours)	76	22.33	3.40 (2.68 - 4.26) *	353.59 (247.35 - 479.81) *	1406	2.25	21.54	10	3.08	3.24 (1.54 - 5.99) *	97.23 (23.61 - 216.17) *	331	1.64	7.17

Table 4. Risk of SMN in patients diagnosed of previous oral cavity cancer

The findings in patients with previous oral cancer (see Table 4) are in the same line as we suspect. In this case we can compare our results with the Italian population. Talking in absolute values, the risk of a SPC in those patients is increased too. Because of sharing similar risk factors, the risk of a SMN at tobacco-susceptible locations is incremented in men of both populations in the oral cavity, larynx, oesophagus, lung, and urinary tract. In this study, we found the limitation that they do not divide pharynx into its sublocations, so their results cannot be compared with ours, but the tendency is the same, with an incremented risk at all its sublocations and in pharynx in general. At women, because of our small sample, there are not significant results, although there are registered cases, with a special mention to the slightly incremented risk at AIRTUM of SMN at mammary glands, with a few cases registered in Girona.

SALIVARY GLANDPRIMARY CANCER																	
	MEN								WOMEN								
	GIRONA CANCER REGISTRY				SEER				GIRONA CANCER REGISTRY				SEER			
SECOND TUMORAL TYPE	OBS	EXP	SIR (CI 95%)	EAR (CI 95%)	OBS	EXP	SIR	EAR	OBS	EXP	SIR (CI 95%)	EAR (CI 95%)	OBS	EXP	SIR	EAR
Lip	2	0.03	75.15 (7.08 - 276.38) *	92.77 (7.61 - 344.51) *	11	1.61	6.85*	5.02	0	0.01	0.00 (0.00 - 622.25)	-0.17 (-0.17 - 106.70)	0	0.25	0.00	-0.12
Oral cavity	0	0.02	0.00 (0.00 - 260.25)	-0.71 (- 0.71 - 183.58)	No data				0	0.01	0.00 (0.00 - 296.93)	-0.36 (-0.36 - 106.51)	No data			
Salivary gland	0	0.00	0.00 (0.00 - 976.30)	-0.19 (- 0.19 - 184.10)	3	0.78	3.86	1.19	0	0.00	0.00 (0.00 - 933.47)	-0.11 (-0.11 - 106.75)	8	0.42	18.94*	3.67
Oropharynx	0	0.01	0.00 (0.00 - 486.06)	-0.38 (- 0.38 - 183.91)	0	0.26	0.00	-0.14	0	0.00	0.00 (0.00 - 999.99)	-0.06 (-0.06 - 106.80)	0	0.09	0.00	-0.04
Nasopharynx	0	0.00	0.00 (0.00 - 999.99)	-0.08 (- 0.08 - 184.22)	0	0.36	0.00	-0.19	0	0.00	0.00 (0.00 - 999.99)	-0.02 (-0.02 - 106.85)	1	0.16	6.44	0.41
Hypopharynx	1	0.01	142.32 (0.06 - 815.80)	46.68 (- 0.31 - 269.14)	2	0.98	2.04	0.54	0	0.00	0.00 (0.00 - 999.99)	-0.01 (-0.01 - 106.86)	1	0.23	4.31	0.37
Nasal cavities and sinus	0	0.00	0.00 (0.00 - 999.99)	-0.17 (- 0.17 - 184.13)	2	0.47	4.24	0.82	0	0.00	0.00 (0.00 - 999.99)	-0.09 (-0.09 - 106.78)	0	0.28	0.00	-0.13
Larynx	1	0.03	29.82 (0.01 - 170.96)	45.43 (- 1.56 - 267.89)	4	4.53	0.88	-0.28	0	0.00	0.00 (0.00 - 999.99)	-0.03 (-0.03 - 106.83)	0	0.83	0.00	-0.40
Head and neck	4	0.10	40.20 (10.46 - 103.96) *	183.36 (44.23 - 481.54) *	No data				0	0.03	0.00 (0.00 - 124.07)	-0.86 (-0.86 - 106.01)	No data			
Lung	3	0.34	8.81 (1.66 - 26.07) *	125.01 (10.58 - 401.44) *	96	52.98	1.81*	22.97	0	0.06	0.00 (0.00 - 70.79)	-1.51 (-1.51 - 105.36)	31	25.30	1.23	2.76
Mammary gland									3	0.36	8.28 (1.56 - 24.51) *	71.90 (5.54 - 232.20) *	59	59.60	0.99	-0.29
Thyroid	0	0.00	0.00 (0.00- 999.99)	-0.11 (-0.11- 184.19)	3	1.12	2.68	1.00	1	0.01	71.70 (0.03- 411.01)	26.88 (-0.37- 155.88)	8	2.25	3.56*	2.78
All (excluding no melanoma skin tumours)	9	2.56	3.52 (1.59 - 6.70) *	302.74 (71.48 - 686.26) *	407	308.54	1.32*	52.58	5	1.71	2.93 (0.92 - 6.89)	89.79 (-3.50 - 274.10)	237	205.14	1.16*	15.41

Table 5. Risk of SMN in patients diagnosed of previous salivary gland cancer

In patients with previous salivary gland cancer (Table 5), we find again that the risk of a SMN is incremented at any location in both sexes. Here we can compare our results with USA population (SEER). The risk of a SPC of the lip or lung is incremented at men of both populations but, at female population, we find some differences: while at Girona population, risk at mammary glands is incremented, at the USA the risk is increased in thyroid gland. It could be maybe because of the differences of the irradiation zones, using at Girona a smaller irradiation field.

NASOPHARYNX PRIMARY CANCER																	
	MEN								WOMEN								
	GIRONA CANCER REGISTRY				SEER				GIRONA CANCER REGISTRY				SEER			
SECOND TUMORAL TYPE	OBS	EXP	SIR (CI 95%)	EAR (CI 95%)	OBS	EXP	SIR	EAR	OBS	EXP	SIR (CI 95%)	EAR (CI 95%)	OBS	EXP	SIR	EAR
Lip	0	0.07	0.00 (0.00 - 55.37)	-1.60 (- 1.60 - 87.01)	0	0.53	0.00	-0.43	0	0.00	0.00 (0.00 - 999.99)	-0.30 (-0.30 - 362.56)	0	0.04	0.00	-0.07
Oral cavity	0	0.05	0.00 (0.00 - 78.21)	-1.13 (- 1.13 - 87.47)	No data				0	0.01	0.00 (0.00 - 628.75)	-0.58 (-0.58 - 362.28)	No data			
Salivary glands	0	0.01	0.00 (0.00 - 352.31)	-0.25 (- 0.25 - 88.36)	1	0.32	3.14	0.55	0	0.00	0.00 (0.00 - 999.99)	-0.18 (-0.18 - 362.69)	0	0.10	0.00	-0.16
Oropharynx	0	0.04	0.00 (0.00 - 111.31)	-0.80 (- 0.80 - 87.81)	0	0.12	0.00	-0.10	0	0.00	0.00 (0.00 - 999.99)	-0.14 (-0.14 - 362.72)	0	0.02	0.00	-0.03
Nasopharynx	0	0.01	0.00 (0.00 - 571.09)	-0.16 (- 0.16 - 88.45)	2	0.59	3.41	1.15	0	0.00	0.00 (0.00 - 999.99)	-0.04 (-0.04 - 362.83)	0	0.10	0.00	-0.16
Hypopharynx	0	0.03	0.00 (0.00 - 136.51)	-0.65 (- 0.65 - 87.96)	0	0.54	0.00	-0.44	0	0.00	0.00 (0.00 - 999.99)	-0.01 (-0.01 - 362.85)	0	0.06	0.00	-0.09
Nasal cavities and sinus	0	0.01	0.00 (0.00 - 401.34)	-0.22 (- 0.22 - 88.39)	3	0.25	11.9 8*	2.24	0	0.00	0.00 (0.00 - 999.99)	-0.10 (-0.10 - 362.76)	1	0.07	13.83	1.44
Larynx	0	0.12	0.00 (0.00 - 32.97)	-2.69 (- 2.69 - 85.92)	3	2.03	1.48	0.79	0	0.00	0.00 (0.00 - 999.99)	-0.06 (-0.06 - 362.80)	0	0.20	0.00	-0.31
Head and neck	0	0.33	0.00 (0.00 - 11.82)	-7.49 (- 7.49 - 81.11)	No data				0	0.02	0.00 (0.00 - 257.84)	-1.41 (-1.41 - 361.45)	No data			
Oesophagus	1	0.09	11.3 (0.00- 64.78)	20.60 (- 1.99- 127.56)	3	2.54	1.18	0.45	0	0.00	0.00 (0.00 - 999.99	-0.30 (-0.30 - 362.57)	3	0.57	5.24*	3.02
Lung	1	1.01	0.99 (0.00- 5.69)	-0.18 (- 22.77- 106.78)	62	23.49	2.64*	31.35	0	0.03	0.00 (0.00- 132.47)	-2.74 (-2.74- 360.22)	13	5.98	2.17*	10.94
Mammary gland									2	0.18	10.90 (1.03 - 40.07) *	168.12 (0.46 - 663.79) *	19	14.72	1.29	6.66
All (excluding no melanoma skin tumours)	5	7.05	0.71 (0.22 - 1.67)	-46.41 (- 123.76 - 106.40)	188	130.60	1.44*	46.73	3	0.83	3.63 (0.68 - 10.74)	201.15 (- 24.17 - 745.42)	79	48.88	1.62*	46.90

Table 6. Risk of SMN in patients diagnosed of previous nasopharynx cancer

We found differences between USA and Girona populations in nasopharynx primary cancer cases (Table 6): in our midst there are no significant results to establish that there is an incremented risk of a SMN at any location, but it was found at the USA, where it is also increased at lung in both sexes and oesophagus in women, while the risk of a SMN is incremented at women of our population.

OROPHARYNX PRIMARY CANCER									
	MEN					WOMEN			
SECOND TUMORAL TYPE	OBS	EXP	SIR (CI 95%)	EAR (CI 95%)		OBS	EXP	SIR (CI 95%)	EAR (CI 95%)
Lip	0	0.09	0.00 (0.00 - 41.42)	-1.70 (-1.70 - 68.88)		0	0.00	0.00 (0.00 - 999.99)	-0.35 (-0.35 - 422.60)
Oral cavity	2	0.07	30.35 (2.86 - 111.62) *	34.82 (2.21 - 131.23) *		0	0.01	0.00 (0.00 - 560.21)	-0.75 (-0.75 - 422.19)
Salivary gland	0	0.02	0.00 (0.00 - 240.13)	-0.29 (-0.29 - 70.29)		0	0.00	0.00 (0.00 - 999.99)	-0.27 (-0.27 - 422.67)
Oropharynx	0	0.04	0.00 (0.00 - 91.97)	-0.77 (-0.77 - 69.81)		0	0.00	0.00 (0.00 - 999.99)	-0.09 (-0.09 - 422.86)
Nasopharynx	0	0.01	0.00 (0.00 - 564.54)	-0.13 (-0.13 - 70.46)		0	0.00	0.00 (0.00 - 999.99)	-0.01 (-0.01 - 422.93)
Hypopharynx	1	0.03	32.75 (0.01 - 187.74)	17.45 (-0.54 - 102.65)		0	0.00	Nan (0.00 - 999.99)	0.00 (0.00 - 422.95)
Nasal cavities and sinus	0	0.01	0.00 (0.00 - 356.91)	-0.20 (-0.20 - 70.38)		0	0.00	0.00 (0.00 - 999.99)	-0.15 (-0.15 - 422.80)
Larynx	4	0.14	29.26 (7.61 - 75.67) *	69.55 (16.27 - 183.75) *		0	0.00	0.00 (0.00 - 999.99)	-0.06 (-0.06 - 422.89)
Head and neck	7	0.40	17.30 (6.86 - 35.85) *	118.74 (42.67 - 253.84) *		0	0.02	0.00 (0.00 - 251.68)	-1.68 (-1.68 - 421.27)
Oesophagus	5	0.11	46.96 (14.82 - 110.46) *	88.10 (26.49 - 209.83) *		1	0.00	303.51 (0.12 - 999.99)	107.53 (-0.31 - 618.06)
Lung	15	1.28	11.71 (6.53 - 19.36) *	247.00 (127.62 - 423.44) *		0	0.03	0.00 (0.00 - 148.24)	-2.85 (-2.85 - 420.09)
All (excluding no melanoma skin tumours)	35	9.13	3.83 (2.67 - 5.33) *	465.70 (274.23 - 712.72) *		3	0.82	3.64 (0.69 - 10.77)	234.66 (-27.97 - 869.06)

Table 7. Risk of SMN in patients diagnosed of previous oropharynx cancer

At our male population with a previous oropharynx cancer presented a higher risk of developing a SMN in general, and specifically (Table 7) at oral cavity, larynx, head and neck, oesophagus and lung.

HYPOPHARYNX PRIMARY CANCER									
	MEN					WOMEN			
SECOND TUMORAL TYPE	OBS	EXP	SIR (CI 95%)	EAR (CI 95%)		OBS	EXP	SIR (CI 95%)	EAR (CI 95%)
Lip	1	0.11	8.70 (0.00 - 49.85)	12.81 (-1.66 - 81.33)		0	0.00	0.00 (0.00 - 999.99)	-0.22 (-0.22 - 764.15)
Oral cavity	0	0.07	0.00 (0.00 - 57.52)	-0.99 (-0.99 - 55.77)		0	0.00	0.00 (0.00 - 999.99)	-0.49 (-0.49 - 763.88)
Salivary gland	0	0.02	0.00 (0.00 - 168.52)	-0.34 (-0.34 - 56.42)		0	0.00	0.00 (0.00 - 999.99)	-0.11 (-0.11 - 764.26)
Oropharynx	0	0.04	0.00 (0.00 - 93.33)	-0.61 (-0.61 - 56.15)		0	0.00	0.00 (0.00 - 999.99)	-0.07 (-0.07 - 764.30)
Nasopharynx	0	0.01	0.00 (0.00 - 701.69)	-0.08 (-0.08 - 56.68)		0	0.00	0.00 (0.00 - 999.99)	-0.02 (-0.02 - 764.35)
Hypopharynx	0	0.03	0.00 (0.00 - 142.54)	-0.40 (-0.40 - 56.36)		0	0.00	0.00 (0.00 - 999.99)	-0.02 (-0.02 - 764.35)
Nasal cavities and sinus	0	0.01	0.00 (0.00 - 314.32)	-0.18 (-0.18 - 56.58)		0	0.00	0.00 (0.00 - 999.99)	-0.05 (-0.05 - 764.32)
Larynx	0	0.15	0.00 (0.00 - 26.22)	-2.16 (-2.16 - 54.60)		0	0.00	0.00 (0.00 - 999.99)	-0.06 (-0.06 - 764.31)
Head and neck	1	0.44	2.25 (0.00 - 12.93)	8.06 (-6.41 - 76.57)		0	0.01	0.00 (0.00 - 742.89)	-1.03 (-1.03 - 763.34)
Oesophagus	5	0.11	43.67 (13.78 - 102.72) *	70.73 (21.18 - 168.62) *		2	0.00	139.59 (131.59 - 999.99) *	389.66 (36.48 - 1433.78) *
Colon	5	1.18	4.24 (1.34 - 9.97) *	55.30 (5.76 - 153.20) *		0	0.04	0.00 (0.00 - 89.04)	-8.58 (-8.58 - 755.78)
Lung	20	1.45	13.76 (8.39 - 21.29) *	268.52 (155.52 - 426.95) *		0	0.01	0.00 (0.00 - 402.35)	-1.90 (-1.90 - 762.47)
All (excluding no melanoma skin tumours)	40	10.81	3.70 (2.64 - 5.04) *	422.58 (257.01 - 632.66) *		2	0.33	6.12 (0.58 - 22.49)	326.18 (-27.01 - 1370.29)

Table 8. Risk of SMN in patients diagnosed of previous hypopharynx cancer

In Girona we found differences between sexes at patients with a previous hypopharynx cancer (Table 8); while men are more likely to have a SMN at oesophagus, colon and lung, presenting an incremented risk at any location, female population has an increased risk to have it at oesophagus.

NASAL CAVITY OR SINUS PRIMARY CANCER																		
	MEN								WOMEN							
	GIRONA CANCER REGISTRY				SEER				GIRONA CANCER REGISTRY				SEER			
SECOND TUMORAL TYPE	OBS	EXP	SIR (CI 95%)	EAR (CI 95%)	OBS	EXP	SIR	EAR	OBS	EXP	SIR (CI 95%)	EAR (CI 95%)	OBS	EXP	SIR	EAR
Lip	0	0.02	0.00 (0.00 - 196.10)	-0.99 (- 0.99 - 193.59)	5	1.01	4.97*	3.87	0	0.00	0.00 (0.00 - 999.99)	-0.08 (- 0.08 - 388.17)	2	0.11	18.53*	2.35
Oral cavity	1	0.01	80.90 (0.03 - 463.76)	49.02 (- 0.59 - 283.90)	No data				0	0.00	0.00 (0.00 - 999.99)	-0.23 (- 0.23 - 388.02)	No data			
Salivary gland	0	0.00	0.00 (0.00 - 999.99)	-0.16 (- 0.16 - 194.43)	2	0.46	4.35	1.49	0	0.00	0.00 (0.00 - 999.99)	-0.08 (- 0.08 - 388.17)	0	0.18	0.00	-0.22
Oropharynx	0	0.01	0.00 (0.00 - 466.17)	-0.42 (- 0.42 - 194.17)	0	0.16	0.00	-0.16	0	0.00	0.00 (0.00 - 999.99)	-0.06 (- 0.06 - 388.20)	1	0.04	24.74	1.19
Nasopharynx	0	0.00	0.00 (0.00 - 999.99)	-0.06 (- 0.06 - 194.53)	0	0.24	0.00	-0.23	0	0.00	0.00 (0.00 - 999.99)	-0.02 (- 0.02 - 388.24)	1	0.07	13.94	1.15
Hypopharynx	0	0.01	0.00 (0.00 - 690.86)	-0.28 (- 0.28 - 194.30)	4	0.63	6.35*	3.26	0	0.00	0.00 (0.00 - 999.99)	-0.01 (- 0.01 - 388.25)	0	0.11	0.00	-0.13
Nasal cavities and sinus	0	0.00	0.00 (0.00 - 999.99)	-0.10 (- 0.10 - 194.48)	4	0.29	13.70*	3.59	0	0.00	0.00 (0.00 - 999.99)	-0.03 (- 0.03 - 388.23)	5	0.13	39.09*	6.06
Larynx	0	0.03	0.00 (0.00 - 131.24)	-1.48 (- 1.48 - 193.10)	8	2.86	2.80*	4.97	0	0.00	0.00 (0.00 - 999.99)	-0.05 (- 0.05 - 388.20)	0	0.38	0.00	-0.47
Head and neck	1	0.08	12.09 (0.00 - 69.28)	45.53 (-4.09 - 280.41)	No data				0	0.01	0.00 (0.00 - 694.47)	-0.56 (- 0.56 - 387.70)	No data			
Oesophagus	0	0.02	0.00 (0.00- 157.52)	-1.24 (- 1.24- 193.35)	3	2.54	1.18	0.45	0	0.01	0.00 (0.00- 516.26)	-0.21 (- 0.21- 106.66)	3	0.57	5.24*	3.02
Lung	3	0.28	10.67 (2.01 - 31.58) *	134.95 (14.12 - 426.81) *	70	33.37	2.10*	35.44	0	0.01	0.00 (0.00 - 343.92)	-1.13 (- 1.13 - 387.13)	26	11.61	2.24*	17.89
Mammary gland									1	0.01	71.70 (0.03- 411.01)	26.88 (- 0.37- 155.88)	34	25.67	1.32	10.35
All (excluding no melanoma skin tumours)	6	2.00	3.00 (1.08 - 6.57) *	198.49 (7.87 - 553.18) *	260	190.05	1.37*	67.69	1	0.31	3.20 (0.00 - 18.32)	68.05 (-30.95 - 536.71)	145	90.63	1.60*	67.60

Table 9. Risk of SMN in patients diagnosed of previous nasal cavity or sinus cancer

Regarding to patients with a primary nose or sinus cancer (Table 9), the risk of a SMN was increased in both sexes at USA population, but only in men in Girona. Pertinent to HNC sublocations, at USA population there were significant results for SPC at lip and nasal cavities and sinus at both sexes and at hypopharynx and larynx at male population too, while in our study there were no significant results. About distal locations, risk was increased in lung for all groups except for women at Girona.

At larynx (Table 10) we could compare our results with the three studies available (AIRTUM, Jegú et al. and SEER). The risk of a SPC was incremented at any location at all studies that we have available data (Girona, Jegú et al. and SEER). According to head and neck cancer at any location, there were significant results at Girona and France. Specifying at head and sublocations, at men there was an incremented risk at oropharynx and hypopharynx at Girona and USA, but not at nasopharynx and nasal cavities in our midst, maybe again because of our sample limitations. It is interesting that our male population presents a similar increased risk at those locations as female USA population. In Italy there is an established higher risk at pharynx sublocations in both sexes.

According to SPC at non-head and neck locations after a larynx cancer, there was an incremented risk of a SMN at oesophagus at all studies (AIRTUM, SEER and Jegú et al.) in both sexes, but not in our population. This elevated risk is found too at lung at all studies for both sexes except women of our population. We think that those differences could be because of limitations of our sample. At men, the risk at urinary bladder, urinary tract and thyroid is significantly augmented. In these cases, we reckon at the role that radiotherapy and tobacco can play here. The results that we have about non-Hodgkin lymphoma could be ascribed to the factors mentioned before.

About head and neck cancers (Table 11) as a conjunct, we only have data to compare with the European countries. The risk of a SMN at any location of the head and neck was increased in both sexes, and the risk of developing a SPC at any location of the body was incremented at Girona and Italy. Itemizing at head and neck sublocations, at oral cavity the risk of a SMN was significantly increased in Italy in both sexes, while in Girona only in men. This fact is applicable at oropharynx and hypopharynx sublocations in Girona's population. At larynx there were only positive significant results for men at Girona and France.

Regarding to non-head and neck locations after an HNC, at digestive tract, for colorectal cancer, it was found an increased risk for both sexes at Girona, and for men in France, while at oesophagus we found that the risk was elevated in both sexes of all populations. About respiratory organs, the lungs also presented an incremented risk of suffering a SMN after an HNC. Male patients of all three studies presented an incremented risk of a SPC at urinary bladder, and urinary tract at Girona and Italy populations. At Girona population, we detected some varieties respect to the other European countries: at both sexes there was an increased risk of a SMN of the thyroid. In addition to this, men presented a significant risk of SPC of prostate and for non-Hodgkin lymphoma, while women at Girona are more susceptible to suffer a SMN at mammary gland.

Summarizing, we found out in our study that the trend of relationships between HNC and the risk of a SMN is common in many locations. We understand these findings as a confirmation of the role of the risk factors that we mentioned before. This could also be explained by the phenomena of the field cancerization due to the exposure to carcinogenic agents, where a damaged tissue is more susceptible to develop into a malignant neoplasm. In this way, for example, incremented risk of a SMN of lung, oesophagus or urinary bladder after an oral cavity cancer could be explained by the

exposure to tobacco. This situation tends to appear on many tobacco-susceptible locations. The lack of significant results for female population in our midst may be secondary to the lack of cases, probably due to the lower prevalence of smokers.

After comparing our population with a country with similar population traits (Italy), another with a more various population (USA) and a country which collects characteristics from both previous (France) threw us a similar trend, explained by the action of the same risk factors described for each cancer sublocation and its relationship with other distal locations with the same susceptibility to that factor. Nonetheless, we found differences between populations. These differences were more substantial in comparison with the USA population. According to this, we interpret that this could be because of the action of different environmental and lifestyle factors, thinking about the different diets between the USA model and the European (concretely Mediterranean diet) and consequently to the different BMI and the variance about the aggressiveness when primary cancer is treated along the years (keeping in mind that radiotherapy techniques in the 80s covered wider areas that nowadays). There were some interpopulation differences that may be due to the environmental factors that we have no data.

Besides, we suspect that the fact of discovering a primary cancer promotes a more strictly following of the patients, allowing to detect new cancers that maybe could be asymptomatic for many years. This fact, added to the increase of the 5-year surveillance, might favour the diagnosis of new tumours. That could explain the cases of mammary gland, prostate and thyroid cancers detected. Also, the presence of a previous tumour might influence the compliance of screening programs, that could be the reason why the risk of suffering a colorectal or breast cancer is incremented.

The role of risk factors such as smoking, alcohol, diet or obesity, especially tobacco, which is implicated at many head and neck cancers, but also at lung, oesophagus and urinary bladder, highly preventable in the development of SMN, which represent up to one in six diagnosed cancers, makes us rethink the importance of insisting on their control, forming part of primary prevention programs for these second neoplasms. This is also applicable to radiotherapy, highlighting the importance of developing new techniques involving smaller irradiation fields.

We recognize that our study is limited by the size of our sample in comparison with the other studies that were made at a national level, the lack of information related to primary cancer and SMN classification (especially at SEER and AIRTUM studies). In addition, we have no information about treatments received, smoking or not status or HPV confirmation, diet, BMI or race and other facts than they can influence. All these facts make it a distant vision but, with the advantage and the security to be a population-based study.

LARYNX PRIMARY CANCER

		MEN																WOMEN															
		GIRONA CANCER REGISTRY				SEER				AIRTUM			JEGU				GIRONA CANCER REGISTRY				SEER				AIRTUM			JEGU			
SECOND TUMORAL TYPE		OBS	EXP	SIR (CI 95%)	EAR (CI 95%)	OBS	EXP	SIR	EAR	OBS	SIR	EAR	OBS	EXP	SIR	EAR (CI 95%)	OBS	EXP	SIR (CI 95%)	EAR (CI 95%)	OBS	EXP	SIR	EAR	OBS	SIR	EAR	OBS	EXP	SIR	EAR (CI 95%)
Lip		1	0.53	1.88 (0.00 - 10.77)	1.18 (-1.34 - 13.13)	17	14.07	1.21	0.23	No data			No data				0	0.00	0.00 (0.00 - 826.78)	-0.26 (-0.26 - 212.20)	0	0.39	0.00	-0.14	No data			No data			
Oral cavity		3	0.31	9.64 (1.82 - 28.53) *	6.79 (0.64 - 21.64) *	No data				136	5.15	0.86	No data				0	0.01	0.00 (0.00 - 407.36)	-0.52 (-0.52 - 211.93)	No data				7	7.61	0.51	No data			
Salivary glands		1	0.10	10.18 (0.00 - 58.33)	2.28 (-0.25 - 14.23)	12	6.36	1.89	0.44	No data			No data				0	0.00	0.00 (0.00 - 999.99)	-0.20 (-0.20 - 212.26)	3	0.67	4.47	0.83	No data			No data			
Pharynx	Oropharynx	3	0.19	15.97 (3.01 - 47.27) *	7.10 (0.95 - 21.95) *	13	2.44	5.34*	0.83	88	3.62	0.50	No data				0	0.00	0.00 (0.00 - 999.99)	-0.10 (-0.10 - 212.36)	5	0.17	28.92*	1.71	7	18.06	0.55	No data			
	Nasopharynx	0	0.03	0.00 (0.00 - 146.71)	-0.07 (-0.07 - 9.83)	8	2.81	2.84*	0.41				No data				0	0.00	0.00 (0.00 - 999.99)	-0.03 (-0.03 - 212.43)	2	0.25	8.15	0.62				No data			
	Hypopharynx	3	0.13	22.23 (4.19 - 65.79) *	7.23 (1.09 - 22.08) *	48	9.37	5.12*	3.02				No data				0	0.00	0.00 (0.00 - 999.99)	-0.01 (-0.01 - 212.44)	8	0.48	16.50*	2.67				No data			
Nasal cavities and sinus		0	0.06	0.00 (0.00 - 62.96)	-0.16 (-0.16 - 9.74)	19	3.99	4.76*	1.17	No data			No data				0	0.00	0.00 (0.00 - 999.99)	-0.12 (-0.12 - 212.33)	1	0.47	2.12	0.19	No data			No data			
Larynx		0	0.69	0.00 (0.00 - 5.66)	-1.75 (-1.75 - 8.15)	50	43.04	1.16	0.55	1	0.02	-0.49	No data				0	0.00	0.00 (0.00 - 999.99)	-0.04 (-0.04 - 212.42)	10	1.12	5.83*	2.94	0	0.00	-0.04	No data			
Head and neck		11	2.05	5.37 (2.67 - 9.65) *	22.61 (8.62 - 44.70) *	No data				225	1.96	0.86	138	15.78	8.75	61.4 (50.3-74.0)	0	0.02	0.00 (0.00 - 167.54)	-1.27 (-1.27 - 211.19)	No data				14	8.00	1.02	10	0.22	45.47*	49.0 (22.9-91.1)
Oesophagus		4	2.25	1.78 (0.46 - 4.60)	4.42 (-3.05 - 20.44)	136	37.96	3.58*	7.68	162	5.68	1.05	64	7.59	8.43	28.3 (21.0-37.3)	0	0.00	0.00 (0.00 - 826.78)	-0.26 (-0.26 - 212.20)	32	2.42	13.24*	10.51	8	12.32	0.61	3	0.11	26.7*	14.5 (2.5-43.4)
Colon		13	5.56	2.34 (1.24 - 4.01) *	18.77 (3.36 - 42.24) *	297	248.42	1.20*	3.80	231	0.97	-0.05	No data				0	0.18	0.00 (0.00 - 22.37)	-9.50 (-9.50 - 202.96)	42	38.43	1.09	1.27	18	1.22	0.27	No data			
Rectum		3	2.26	1.33 (0.25-3.93)	1.88 (-4.27-16.72)	100	103.97	0.96	-0.31	115	1.04	0.03	No data				1	0.06	16.25 (0.01-93.15)	50.86 (-3.31-307.31)	13	7.96	1.63	1.79	17	2.93	0.93	No data			
Colon, rectum and anus		16	7.82	2.05 (1.17 - 3.33) *	20.65 (3.28 - 46.00) *	No data				346	0.99	-0.02	62	39.40	1.57	11.4 (4.1-20.1)	1	0.24	4.22 (0.00 - 24.20)	41.36 (-12.81-97.81)	No data				35	1.70*	1.20	No data			
Lung		60	6.76	8.88 (6.78 - 11.44) *	134.44 (98.53 - 178.04) *	1657	493.46	3.36*	91.10	1602	3.41	8.87	310	44.71	6.93	133.3 (116.5-151.7)	0	0.04	0.00 (0.00 - 94.33)	-2.25 (-2.25 - 210.20)	350	48.47	7.16*	106.94	82	9.52*	6.11	19	0.74	25.76	91.5 (53.6-145.0)
Prostate		22	12.01	1.83 (1.15 - 2.78) *	25.22 (4.43 - 53.90) *	762	866.46	0.88*	-8.18	418	0.85	-0.56	No data																		
Mammary gland																	1	0.26	3.81 (0.00-21.83)	39.96 (-14.21-296.41)	114	101.75	1.12	4.35	44	1.27	0.78	No data			
Urinary bladder		12	6.02	1.99 (1.02 - 3.49) *	15.09 (0.37 - 37.88) *	252	189.24	1.33*	4.91	477	1.73	1.58	46	16025	2.83	15.0 (8.8-22.7)	0	0.05	0.00 (0.00 - 71.95)	-2.95 (-2.95 - 209.50)	11	9.66	1.14	0.48	6	1.28	0.11	No data			
Urinary tract		13	6.29	2.07 (1.10 - 3.55) *	16.95 (1.53 - 40.41) *	353	262.66	1.34*	7.07	489	1.70	1.58	No data				0	0.06	0.00 (0.00 - 64.77)	-3.28 (-3.28 - 209.18)	25	16.77	1.49	2.92	6	1.19	0.08	No data			
Thyroid		2	0.06	33.69 (3.18 - 123.89) *	4.90 (0.33 - 18.42) *	19	8.32	2.28*	0.84	50	4.47	0.30	No data				0	0.01	0.00 (0.00 - 507.22)	-0.42 (-0.42 - 212.04)	6	2.95	2.03	1.08	6	2.54	0.30	No data			
Non-Hodgkin lymphoma		8	1.04	7.70 (3.29 - 15.25) *	17.58 (6.00 - 37.37) *	97	83.30	1.16	1.07	89	1.23	0.13	No data				0	0.03	0.00 (0.00 - 124.19)	-1.71 (-1.71 - 210.74)	16	12.83	1.25	1.13	4	0.79	-0.09	No data			
All (excluding no melanoma skin tumours)		161	50.71	3.18 (2.70 - 3.71) *	278.48 (218.11 - 346.42) *	4,427	2,734.88	1.62*	132.49	4225	1.672.25	13.32	No data				2	1.28	1.56 (0.15 - 5.74)	38.95 (-59.21-329.16)	850	352.54	2.41*	176.67	257	1.91	10.21	No data			

Table 10. Risk of SMN in patients diagnosed of previous larynx cancer

HEAD AND NECK PRIMARY CANCER																								
		MEN												WOMEN										
		GIRONA CANCER REGISTRY				AIRTUM			JEGU				GIRONA CANCER REGISTRY				AIRTUM			JEGU			
SECOND TUMORAL TYPE		OBS	EXP	SIR (CI 95%)	EAR (CI 95%)	OBS	SIR	EAR	OBS	EXP	SIR	EAR (CI 95%)	OBS	EXP	SIR (CI 95%)	EAR (CI 95%)	OBS	SIR	EAR	OBS	EXP	SIR	EAR (CI 95%)
Lip		4	1.26	3.17 (0.83 - 8.20)	2.84 (-0.23 - 9.42)	No data			No data				0	0.03	0.00 (0.00 - 122.25)	-0.17 (-0.17 - 20.33)	No data			No data			
Oral cavity		9	0.76	11.80 (5.35 - 22.49) *	8.55 (3.44 - 17.01) *	284	7.26*	1.26	No data				1	0.07	14.99 (0.01 - 85.93)	4.88 (-0.35 - 29.62)	58	20.08*	1.41	No data			
Salivary gland		1	0.22	4.50 (0.00 - 25.79)	0.81 (-0.23 - 5.72)	No data			No data				0	0.02	0.00 (0.00 - 173.99)	-0.12 (-0.12 - 20.38)	No data			No data			
Pharynx	Oropharynx	9	0.48	18.92 (8.58 - 36.07) *	8.84 (3.74 - 17.31) *	172	4.73	0.70	No data				0	0.01	0.00 (0.00 - 331.79)	-0.06 (-0.06 - 20.43)	18	14.77	0.43	No data			
	Nasopharynx	0	0.07	0.00 (0.00 - 54.90)	-0.07 (-0.07 - 3.99)				No data				0	0.00	0.00 (0.00 - 999.99)	-0.02 (-0.02 - 20.48)				No data			
	Hypopharynx	7	0.34	20.46 (8.11 - 42.39) *	6.91 (2.52 - 14.69) *				No data				0	0.00	0.00 (0.00 - 999.99)	-0.01 (-0.01 - 20.49)				No data			
Nasal cavities and sinus		0	0.14	0.00 (0.00 - 27.45)	-0.15 (-0.15 - 3.92)	No data			No data				0	0.01	0.00 (0.00 - 300.42)	-0.07 (-0.07 - 20.43)	No data			No data			
Larynx		12	1.70	7.08 (3.64 - 12.40) *	10.69 (4.64 - 20.06) *	263	2.84	0.88	76	10.74	7.07	16.8 (12.7-21.8)	1	0.01	171.76 (0.07 - 984.56)	5.20 (-0.03 - 29.93)	28	20.92	0.68	No data			
Head and neck		42	4.97	8.44 (6.08 - 11.42) *	38.42 (26.23 - 53.79) *	719	4.28*	2.84	405	24.54	16.50	98.2 (88.3-108.9)	2	0.16	12.77 (1.20 - 46.95) *	9.64 (0.17 - 37.63) *	104	19.10*	2.52	57	0.61	93.83	72.5 (54.7-94.1)
Oesophagus		24	1.25	19.13 (12.24 - 28.50) *	23.60 (14.63 - 35.80) *	477	11.52*	2.25	269	13.79	19.51	65.9 (57.8-74.7)	4	0.04	110.26 (28.68 - 285.11) *	20.72 (5.25 - 53.88) *	48	23.61*	1.18	20	0.41	49.33	25.2 (15.2-39.2)
Colon		29	13.08	2.22 (1.48 - 3.19) *	16.52 (6.57 - 29.69) *	347	1.03	0.05	No data				2	1.15	1.74 (0.16 - 6.41)	4.46 (-5.01 - 32.45)	46	1.00	0.00	No data			
Rectum		12	5.39	2.23 (1.15 - 3.90) *	6.86 (0.81 - 16.23) *	180	1.14	0.11	No data				3	0.42	7.13 (1.35 - 21.12) *	13.48 (0.76 - 44.22) *	32	1.78	0.36	No data			
Colon, rectum and anus		41	18.46	2.22 (1.59 - 3.01) *	23.38 (11.36 - 38.60) *	527	1.06	0.16	109	60.09	1.81	12.6 (7.6-18.4)	5	1.57	3.19 (1.01 - 7.50) *	17.94 (0.05 - 53.28) *	78	1.22	0.36	No data			
Lung		149	16.24	9.18 (7.76 - 10.78) *	137.75 (113.93 - 164.69) *	149	3.63*	9.04	663	76.15	8.71	151.5 (138.7-165.1)	1	0.28	3.60 (0.00 - 20.62)	3.77 (-1.45 - 28.51)	192	7.30*	4.24	51	2.71	18.81	62.1 (45.3-82.7)
Prostate		46	28.43	1.62 (1.18 - 2.16) *	18.23 (5.43 - 34.20) *	602	0.87	-0.48	No data														
Mammary gland													9	1.75	5.13 (2.33 - 9.78) *	37.88 (12.16 - 80.53) *	145	1.33	0.93	No data			
Urinary bladder		27	14.14	1.91 (1.26 - 2.78) *	13.35 (3.78 - 26.14) *	642	1.65*	1.30	53	24.13	2.20	7.5 (4.0-11.7)	0	0.35	0.00 (0.00 - 11.19)	-1.83 (-1.83 - 18.66)	17	1.17	0.06	No data			
Urinary tract		29	14.77	1.96 (1.31 - 2.82) *	14.77 (4.81 - 27.94) *	662	1.63*	1.32	No data				0	0.39	0.00 (0.00 - 9.94)	-2.06 (-2.06 - 18.43)	17	1.09	0.04	No data			
Thyroid		3	0.15	20.00 (3.77 - 59.19) *	2.96 (0.43 - 9.06) *	79	4.64	0.32	No data				2	0.06	33.60 (3.17 - 123.58) *	10.14 (0.67 - 38.14) *	21	2.68	0.34	No data			
Non-Hodgkin lymphoma		12	2.47	4.85 (2.50 - 8.50) *	9.88 (3.84 - 19.25) *	139	1.33	0.18	No data				0	0.23	0.00 (0.00 - 16.96)	-1.21 (-1.21 - 19.29)	23	1.48	0.19	No data			
All (excluding no melanoma skin tumours)		390	120.01	3.25 (2.94 - 3.59) *	280.13 (240.97 - 322.38) *	6262	1.78*	14.14	No data				30	8.53	3.52 (2.37 - 5.02) *	112.22 (61.12 - 179.51) *	718	1.73*	7.77	No data			

Table 11. Risk of SMN in patients diagnosed of previous head and neck cancer

CONCLUSIONS

1. Our study found out that risk of a SMN in patients with a previous HNC was increased in both sexes.

2. There was a repetitive fact which consisted on the increase of risk at distal locations like oesophagus, lung and urinary tract. All those cancer types are considered tobacco-related.

3. The findings after comparing our population with populations from other countries threw us a similar trend. There were some interpopulation differences that may be due to the environmental factors that we have no data.

4. The role of highly preventable risk factors in the development of SMN, makes us rethink the importance of insisting on their control, forming part of primary prevention programs for these second neoplasms.

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) tutor (Jordi Rubió Casadevall) to decide about the topic of the final degree project (FDP) (D1-D3, D6-D10).

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

Activity 3. Formation about biostatistics concepts: SIR and EAR analysis. (D4-D5, D10-D13)

Data collect (PHASE 1)

Activity 4. Data collection (D14-16)

Activity 5. Debugging database (D17-D21)

Analyses and final evolution (PHASE 2)

Activity 6. Analyse of results at local and distal locations (D17-D35)

Activity 7. Analyse of other populations (D22-D37)

Activity 8. Comparison between populations (D38-D40)

Activity 9. Final degree project writing (D6-55)

Activity 10. Data validation (D60-D67)

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

CHRONOGRAM												
Days September 2018	12	13	14	15	16	17	18	19	20	21	22	23
PHASE 0. Researchers: Jordi Rubió, Rafael Marcos, José Andrés Marchena												
Meetings with the FDP advisor	■	■	■			■	■	■	■	■		
Meeting with the director of GCR						■	■	■	■	■		
Formation				■	■					■	■	■
Days September 2018	24	25	26	27	28	29	30					
PHASE 1. Researchers: Jordi Rubió, Rafael Marcos, José Andrés Marchena												
Data collection	■	■	■									
Debugging database				■	■	■	■					

Months (2018-2019)	September	October	November	December	January	February	March
PHASE 2. Researchers: José Andrés Marchena							
Analyse of results at local and distal locations	■	■					
Analyse of other populations		■					
Comparison between populations		■	■				
FDP writing	■	■	■				
Data validation			■				
Result dissemination, writing scientific papers and publication				■	■	■	■

Table 12. Chronogram of the FDP

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 alternative project if we had to build all the database and registering all the exposure to different risk factors at each patient by reviewing patients' health records.

BUDGET	
ACTIVITES	**COSTS**
Staff	**Subtotal: 1520€**
-Meetings and formation: 500€x3 members -Prints	-1500€ -20€
Statistical Analysis	**Subtotal: 55.160€**
-Reviewing patients' health records: 2748 patients/each patient's health record 20€ -Statistical team: 20€/h, a total of 10h for this final degree project	-54.960€ -200€
Travel and subsistence costs	**Subtotal: 1700€**
-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€
Publication	**Subtotal: 1550€**
-Paper revision -Paper publication (*Cancer epidemiology*)	-50€ -1500€
	TOTAL: 59.930€

Table 13. Calculation of the cost of the study

Annex 1.- International rules for multiple primary cancers (ICD-O-3)

IACR

IARC

ENCR

International Agency for Research on Cancer
World Health Organization
International Association of Cancer Registries
European Network of Cancer Registries

INTERNATIONAL RULES FOR MULTIPLE PRIMARY CANCERS (ICD-O Third Edition)

IARC, Lyon, 2004

Internal Report No. 2004 / 02

WORKING GROUP

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MULTIPLE PRIMARY NEOPLASMS

Cancer registries use different rules for defining multiple primaries when registering cancer cases. The rules given here are for **reporting** data on cancer incidence and survival, so that cancer risk and outcome are comparable between different populations.

For **collection**, it is recommended that registries collect and register more detailed data and some suggestions are given in the Recommendations for Recording which follow. Such cases should be collapsed to conform to the international rules for analysis.

RULES FOR REPORTING INCIDENCE AND SURVIVAL

1. The recognition of the existence of two or more primary cancers does not depend on time.

2. A primary cancer is one that originates in a primary site or tissue and is not an extension, nor a recurrence, nor a metastasis.

3. Only one tumour shall be recognised as arising in an organ or pair of organs or tissue.
Some groups of codes are considered to be a single organ for the purposes of defining multiple tumours. These topography code groups are shown in Table 1.

Multifocal tumours – that is, discrete masses apparently not in continuity with other primary cancers originating in the *same* primary site or tissue, for example bladder – are counted as a single cancer.

4. Rule 3 does not apply in two circumstances:

4.1 Systemic (or multicentric) cancers potentially involving many different organs are only counted once in any individual. These are Kaposi sarcoma (group 15 in Table 2) and tumours of the haematopoietic system (groups 8-14 in Table 2).

4.2 Neoplasms of different morphology should be regarded as multiple cancers (even if they are diagnosed simultaneously in the same site).

If the morphological diagnoses fall into one category in Table 2, and arise in the same primary site, they are considered to be the same morphology for the purpose of counting multiple primaries. If the morphological diagnoses fall into two or more of the categories in Table 2, even if they concern the same site, the morphology is considered to be different, and two or more cases should be counted.

Single tumours containing several different histologies which fall into one histological group in Table 2 are registered as a single case, using the numerically highest ICD-O morphology code.

If, however, one morphology is not specific (groups (5), (14) and (17)) and a specific morphology is available, the case should be reported with the specific histology and the non-specific diagnosis should be ignored.

Table 1. Groups of topography codes considered a single site in the definition of multiple cancers

ICD-O-2/3 site code	Label	If diagnosed at different times, code first diagnosis. If diagnosed at the same time use codes given below.
C01	Base of tongue	
C02	Other and unspecified parts of tongue	C02.9
C00	Lip	
C03	Gum	
C04	Floor of mouth	
C05	Palate	
C06	Other and unspecified parts of mouth	C06.9
C09	Tonsil	
C10	Oropharynx	
C12	Pyriform sinus	
C13	Hypopharynx	
C14	Other and ill-defined sites in lip, oral cavity and pharynx	C14.0
C19	Rectosigmoid junction	
C20	Rectum	C20.9
C23	Gallbladder	
C24	Other and unspecified parts of biliary tract	C24.9
C33	Trachea	
C34	Bronchus and lung	C34.9
C40	Bones, joints and articular cartilage of limbs	
C41	Bones, joints and articular cartilage of other and unspecified sites	C41.9
C65	Renal pelvis	
C66	Ureter	
C67	Bladder	
C68	Other and unspecified urinary organs	C68.9

Table 2. Groups of malignant neoplasms considered to be histologically 'different' for the purpose of defining multiple tumours (adapted from Berg JW. Morphologic classification of human cancer. In: Schottenfeld D & Fraumeni JF Jr. *Cancer Epidemiology and Prevention*, 2nd edition, Chapter 3 of Section 1: Basic Concepts. Oxford, New York, Oxford University Press, pp. 28-44, 1996).

Group	
Carcinomas	
1. Squamous and transitional cell carcinoma	8051-8084, 8120-8131
2. Basal cell carcinomas	8090-8110
3. Adenocarcinomas	8140-8149, 8160-8162, 8190-8221, 8260-8337, 8350-8551, 8570-8576, 8940-8941
4. Other specific carcinomas	8030-8046, 8150-8157, 8170-8180, 8230-8255, 8340-8347, 8560-8562, 8580-8671
(5) Unspecified carcinomas (NOS)	8010-8015, 8020-8022, 8050
6. *Sarcomas* and soft tissue tumours	8680-8713, 8800-8921, 8990-8991, 9040-9044, 9120-9125, 9130-9136, 9141-9252, 9370-9373, 9540-9582
7. ***Mesothelioma***	9050-9055
Tumours of haematopoietic and lymphoid tissues	
8. Myeloid	9840, 9861-9931, 9945-9946, 9950, 9961-9964, 9980-9987
9. B-cell neoplasms	9670-9699, 9728, 9731-9734, 9761-9767, 9769, 9823-9826, 9833, 9836, 9940
10. T-cell and NK-cell neoplasms	9700-9719, 9729, 9768, 9827-9831, 9834, 9837, 9948
11. Hodgkin lymphoma	9650-9667
12. Mast-cell Tumours	9740-9742
13. Histiocytes and Accessory Lymphoid cells	9750-9758
(14) Unspecified types	9590-9591, 9596, 9727, 9760, 9800-9801, 9805, 9820, 9832, 9835, 9860, 9960, 9970, 9975, 9989
15. ***Kaposi sarcoma***	9140
16. ***Other specified*** types of cancer	8720-8790, 8930-8936, 8950-8983, 9000-9030, 9060-9110, 9260-9365, 9380- 9539
(17) ***Unspecified*** types of cancer	8000-8005

RECOMMENDATIONS FOR RECORDING

1. Two tumours of different laterality, but of the same morphology, diagnosed in paired organs (e.g. breast) should be registered separately unless stated to have origina- ted from a single primary.

Exceptions to this rule are:

a) Tumours of the ovary (of the same morphology)
b) Wilm's tumour (nephroblastoma) of the kidney.
c) Retinoblastoma

which should be recorded as a single bilateral registration when they occur on both sides.

Reminder: tumours in paired organs of completely different histology should be registered separately.

2. Cancers which occur in any 4th character subcategory of colon (C18) and skin (C44) should be registered as multiple primary cancers.

Annex 2. Risk of a SMN at each location of head and neck at Girona

RISK OF A SMN AT MEN DIAGNOSED WITH PREVIOUS LIP CANCER

SECOND TUMORAL TYPE	OBS	EXP	SIR	SIR (CI 95%)	EAR	EAR (CI 95%)
Lip	0	0.16	0.00	(0.00 - 23.87)	-0.80	(-0.80 - 18.27)
Oral cavity	0	0.09	0.00	(0.00 - 42.47)	-0.45	(-0.45 - 18.61)
Salivary glands	0	0.03	0.00	(0.00 - 136.22)	-0.14	(-0.14 - 18.92)
Oropharynx	2	0.05	37.80	(3.56 - 139.02) *	9.47	(0.66 - 35.51) *
Nasopharynx	0	0.01	0.00	(0.00 - 474.23)	-0.04	(-0.04 - 19.02)
Hypopharynx	0	0.04	0.00	(0.00 - 106.41)	-0.18	(-0.18 - 18.88)
Nasal cavities and sinus	0	0.02	0.00	(0.00 - 239.28)	-0.08	(-0.08 - 18.98)
Larynx	1	0.21	4.82	(0.00 - 27.63)	3.85	(-1.01 - 26.87)
Head and neck	**3**	**0.61**	**4.94**	**(0.93 - 14.63)**	**11.64**	**(-0.20 - 40.23)**
Oesophagus	2	0.15	13.12	(1.24 - 48.26) *	8.98	(0.18 - 35.03) *
Stomach	0	0.69	0.00	(0.00 - 5.66)	-3.37	(-3.37 - 15.69)
Colon	3	1.71	1.76	(0.33 - 5.20)	6.28	(-5.55 - 34.88)
Rectum	4	0.67	5.98	(1.56 - 15.47) *	16.20	(1.81 - 47.04) *
Colon, rectum and anus	7	2.38	2.95	(1.17 - 6.10) *	22.48	(1.94 - 58.97) *
Liver	1	0.38	2.64	(0.00 - 15.14)	3.02	(-1.84 - 26.03)
Gallbladder and pathways	0	0.17	0.00	(0.00 - 22.86)	-0.83	(-0.83 - 18.23)
Pancreas	1	0.35	2.86	(0.00 - 16.40)	3.16	(-1.70 - 26.17)
Lung	18	2.03	8.86	(5.24 - 14.03) *	77.65	(41.88 - 128.72) *
Bone and cartilage	0	0.02	0.00	(0.00 - 247.30)	-0.08	(-0.08 - 18.99)
Skin melanoma	1	0.18	5.43	(0.00 - 31.13)	3.97	(-0.89 - 26.98)
Soft tissues	0	0.07	0.00	(0.00 - 56.90)	-0.34	(-0.34 - 18.73)
Prostate	9	3.64	2.47	(1.12 - 4.71) *	26.05	(2.13 - 65.73) *
Testicle	0	0.01	0.00	(0.00 - 486.65)	-0.04	(-0.04 - 19.02)
Kidney	1	0.31	3.20	(0.00 - 18.32)	3.34	(-1.52 - 26.35)
Urinary bladder	6	1.82	3.30	(1.19 - 7.22) *	20.32	(1.65 - 55.07) *
Pelvis, ureter and pathways	0	0.08	0.00	(0.00 - 48.36)	-0.39	(-0.39 - 18.67)
Urinary tract	6	1.90	3.16	(1.14 - 6.91) *	19.93	(1.25 - 54.68) *
Encephalon and CNS	1	0.15	6.58	(0.00 - 37.71)	4.12	(-0.74 - 27.14)
Thyroid	0	0.02	0.00	(0.00 - 238.95)	-0.08	(-0.08 - 18.98)
Hodgkin Lymphoma	0	0.02	0.00	(0.00 - 184.62)	-0.10	(-0.10 - 18.96)
Non-Hodgkin Lymphoma	3	0.32	9.50	(1.79 - 28.11) *	13.05	(1.21 - 41.65) *
Multiple myeloma	0	0.19	0.00	(0.00 - 21.06)	-0.91	(-0.91 - 18.16)
Leukaemia	0	0.45	0.00	(0.00 - 8.78)	-2.17	(-2.17 - 16.89)
Another	5	1.35	3.70	(1.17 - 8.69) *	17.73	(1.09 - 50.61) *
All (excluding no melanoma skin tumours)	**58**	**15.42**	**3.76**	**(2.86 - 4.86) ***	**207.05**	**(139.13 - 289.79) ***

RISK OF A SMN AT WOMEN DIAGNOSED WITH PREVIOUS LIP CANCER

SECOND TUMORAL TYPE	OBS	EXP	SIR	SIR (CI 95%)	EAR	EAR (CI 95%)
Lip	0	0.00	0.00	(0.00 - 999.99)	-0.02	(-0.02 - 131.89)
Oral cavity	1	0.00	1559.76	(0.62 - 999.99)	33.62	(-0.01 - 192.84)
Salivary glands	0	0.00	0.00	(0.00 - 999.99)	-0.01	(-0.01 - 131.89)
Oropharynx	0	0.00	0.00	(0.00 - 999.99)	-0.01	(-0.01 - 131.90)
Nasopharynx	0	0.00	Nan	(0.00 - 999.99)	0.00	(0.00 - 131.90)
Hypopharynx	0	0.00	0.00	(0.00 - 999.99)	0.00	(0.00 - 131.90)
Nasal cavities and sinus	0	0.00	0.00	(0.00 - 999.99)	-0.01	(-0.01 - 131.89)
Larynx	0	0.00	Nan	(0.00 - 999.99)	0.00	(0.00 - 131.90)
Head and neck	**1**	**0.00**	**517.93**	**(0.21 - 999.99)**	**33.58**	**(-0.05 - 192.80)**
Oesophagus	0	0.00	0.00	(0.00 - 999.99)	-0.02	(-0.02 - 131.89)
Stomach	0	0.01	0.00	(0.00 - 333.23)	-0.40	(-0.40 - 131.51)
Colon	0	0.02	0.00	(0.00 - 166.52)	-0.79	(-0.79 - 131.11)
Rectum	0	0.01	0.00	(0.00 - 406.29)	-0.32	(-0.32 - 131.58)
Colon, rectum and anus	0	0.03	0.00	(0.00 - 118.11)	-1.12	(-1.12 - 130.79)
Liver	0	0.00	0.00	(0.00 - 861.79)	-0.15	(-0.15 - 131.75)
Gallbladder and pathways	0	0.01	0.00	(0.00 - 777.94)	-0.17	(-0.17 - 131.73)
Pancreas	0	0.01	0.00	(0.00 - 589.05)	-0.22	(-0.22 - 131.68)
Lung	0	0.01	0.00	(0.00 - 743.47)	-0.18	(-0.18 - 131.73)
Bone and cartilage	0	0.00	0.00	(0.00 - 999.99)	0.00	(0.00 - 131.90)
Skin melanoma	1	0.00	364.73	(0.15 - 999.99)	33.55	(-0.08 - 192.77)
Soft tissues	0	0.00	0.00	(0.00 - 999.99)	-0.02	(-0.02 - 131.88)
Mammary gland	1	0.03	30.25	(0.01 - 173.39)	32.53	(-1.10 - 191.75)
Cervix	0	0.00	0.00	(0.00 - 999.99)	-0.07	(-0.07 - 131.84)
Uterine body	1	0.01	145.75	(0.06 - 835.49)	33.41	(-0.22 - 192.63)
Ovary	0	0.01	0.00	(0.00 - 779.67)	-0.17	(-0.17 - 131.73)
Kidney	0	0.00	0.00	(0.00 - 999.99)	-0.07	(-0.07 - 131.84)
Urinary bladder	0	0.01	0.00	(0.00 - 554.96)	-0.24	(-0.24 - 131.67)
Pelvis, ureter and pathways	0	0.00	0.00	(0.00 - 999.99)	-0.04	(-0.04 - 131.86)
Urinary tract	0	0.01	0.00	(0.00 - 474.99)	-0.28	(-0.28 - 131.63)
Encephalon and CNS	0	0.00	0.00	(0.00 - 999.99)	-0.05	(-0.05 - 131.86)
Thyroid	0	0.00	0.00	(0.00 - 999.99)	-0.03	(-0.03 - 131.88)
Hodgkin Lymphoma	0	0.00	0.00	(0.00 - 999.99)	-0.01	(-0.01 - 131.89)
Non-Hodgkin Lymphoma	0	0.00	0.00	(0.00 - 854.21)	-0.15	(-0.15 - 131.75)
Multiple myeloma	0	0.00	0.00	(0.00 - 999.99)	-0.11	(-0.11 - 131.79)
Leukaemia	0	0.01	0.00	(0.00 - 667.66)	-0.20	(-0.20 - 131.71)
Another	0	0.03	0.00	(0.00 - 153.58)	-0.86	(-0.86 - 131.04)
All (excluding no melanoma skin tumours)	**4**	**0.17**	**23.37**	**(6.08 - 60.44) ***	**128.82**	**(29.25 - 342.24) ***

RISK OF A SMN AT MEN DIAGNOSED WITH PREVIOUS ORAL CAVITY CANCER

SECOND TUMORAL TYPE	OBS	ESP	SIR	SIR (CI 95%)	EAR	EAR (CI 95%)
Lip	0	0.24	0.00	(0.00 - 16.52)	-1.56	(-1.56 - 24.26)
Oral cavity	3	0.15	20.31	(3.83 - 60.13) *	18.79	(2.75 - 57.53) *
Salivary glands	0	0.04	0.00	(0.00 - 105.01)	-0.25	(-0.25 - 25.58)
Oropharynx	4	0.10	40.59	(10.56 - 104.96) *	25.70	(6.20 - 67.49) *
Nasopharynx	0	0.01	0.00	(0.00 - 275.87)	-0.09	(-0.09 - 25.73)
Hypopharynx	2	0.07	28.21	(2.66 - 103.73) *	12.71	(0.77 - 47.99) *
Nasal cavities and sinus	0	0.03	0.00	(0.00 - 155.07)	-0.17	(-0.17 - 25.66)
Larynx	6	0.33	18.35	(6.60 - 40.20) *	37.37	(12.07 - 84.45) *
Head and neck	**15**	**0.96**	**15.65**	**(8.73 - 25.88) ***	**92.50**	**(48.82 - 157.07) ***
Oesophagus	5	0.24	20.99	(6.62 - 49.37) *	31.37	(8.82 - 75.91) *
Stomach	1	0.99	1.01	(0.00 - 5.78)	0.05	(-6.53 - 31.23)
Colon	5	2.41	2.07	(0.65 - 4.87)	17.04	(-5.50 - 61.58)
Rectum	3	1.01	2.97	(0.56 - 8.79)	13.10	(-2.93 - 51.84)
Colon, rectum and anus	8	3.42	2.34	(1.00 - 4.63)	30.14	(-0.05 - 81.80)
Liver	1	0.58	1.72	(0.00 - 9.89)	2.77	(-3.82 - 33.94)
Gallbladder and pathways	0	0.23	0.00	(0.00 - 17.22)	-1.50	(-1.50 - 24.33)
Pancreas	0	0.49	0.00	(0.00 - 7.92)	-3.26	(-3.26 - 22.57)
Lung	29	3.09	9.40	(6.29 - 13.52) *	170.72	(107.51 - 254.36) *
Bone and cartilage	0	0.02	0.00	(0.00 - 169.37)	-0.15	(-0.15 - 25.67)
Skin melanoma	0	0.25	0.00	(0.00 - 15.63)	-1.65	(-1.65 - 24.17)
Soft tissues	0	0.09	0.00	(0.00 - 43.51)	-0.59	(-0.59 - 25.23)
Prostate	6	5.28	1.14	(0.41 - 2.49)	4.76	(-20.54 - 51.83)
Testicle	0	0.02	0.00	(0.00 - 241.35)	-0.11	(-0.11 - 25.72)
Kidney	0	0.46	0.00	(0.00 - 8.43)	-3.06	(-3.06 - 22.76)
Urinary bladder	6	2.61	2.30	(0.83 - 5.04)	22.33	(-2.97 - 69.41)
Pelvis, ureter and pathways	1	0.12	8.52	(0.00 - 48.86)	5.81	(-0.77 - 36.99)
Urinary tract	7	2.73	2.57	(1.02 - 5.32) *	28.14	(0.31 - 77.58) *
Encephalon and CNS	1	0.23	4.41	(0.00 - 25.30)	5.10	(-1.49 - 36.27)
Thyroid	0	0.03	0.00	(0.00 - 127.29)	-0.20	(-0.20 - 25.62)
Hodgkin Lymphoma	0	0.03	0.00	(0.00 - 122.16)	-0.21	(-0.21 - 25.62)
Non-Hodgkin Lymphoma	1	0.46	2.18	(0.00 - 12.52)	3.57	(-3.01 - 34.75)
Multiple myeloma	0	0.27	0.00	(0.00 - 14.41)	-1.79	(-1.79 - 24.04)
Leukaemia	0	0.62	0.00	(0.00 - 6.28)	-4.11	(-4.11 - 21.71)
Another	2	1.78	1.12	(0.11 - 4.13)	1.44	(-10.49 - 36.72)
All (excluding no melanoma skin tumours)	**76**	**22.33**	**3.40**	**(2.68 - 4.26) ***	**353.59**	**(247.35 - 479.81) ***

RISK OF A SMN AT WOMEN DIAGNOSED WITH PREVIOUS ORAL CAVITY CANCER

SECOND TUMORAL TYPE	OBS	ESP	SIR	SIR (CI 95%)	EAR	EAR (CI 95%)
Lip	0	0.01	0.00	(0.00 - 321.61)	-0.17	(-0.17 - 54.94)
Oral cavity	0	0.03	0.00	(0.00 - 155.93)	-0.35	(-0.35 - 54.75)
Salivary glands	0	0.01	0.00	(0.00 - 453.65)	-0.12	(-0.12 - 54.99)
Oropharynx	0	0.00	0.00	(0.00 - 924.70)	-0.06	(-0.06 - 55.05)
Nasopharynx	0	0.00	0.00	(0.00 - 999.99)	-0.02	(-0.02 - 55.09)
Hypopharynx	0	0.00	0.00	(0.00 - 999.99)	-0.01	(-0.01 - 55.10)
Nasal cavities and sinus	0	0.00	0.00	(0.00 - 935.60)	-0.06	(-0.06 - 55.05)
Larynx	1	0.00	554.18	(0.22 - 999.99)	14.03	(-0.02 - 80.55)
Head and neck	**1**	**0.06**	**17.23**	**(0.01 - 98.76)**	**13.24**	**(-0.81 - 79.76)**
Oesophagus	1	0.01	74.90	(0.03 - 429.33)	13.87	(-0.18 - 80.39)
Stomach	0	0.18	0.00	(0.00 - 21.98)	-2.51	(-2.51 - 52.60)
Colon	0	0.42	0.00	(0.00 - 9.39)	-5.87	(-5.87 - 49.24)
Rectum	1	0.15	6.65	(0.00 - 38.12)	11.94	(-2.11 - 78.46)
Colon, rectum and anus	1	0.57	1.76	(0.00 - 10.09)	6.07	(-7.98 - 72.59)
Liver	0	0.07	0.00	(0.00 - 56.71)	-0.97	(-0.97 - 54.14)
Gallbladder and pathways	0	0.08	0.00	(0.00 - 51.94)	-1.06	(-1.06 - 54.05)
Pancreas	0	0.12	0.00	(0.00 - 32.91)	-1.67	(-1.67 - 53.43)
Lung	1	0.10	10.14	(0.00 - 58.14)	12.67	(-1.38 - 79.19)
Bone and cartilage	0	0.00	0.00	(0.00 - 787.79)	-0.07	(-0.07 - 55.04)
Skin melanoma	0	0.06	0.00	(0.00 - 67.73)	-0.81	(-0.81 - 54.29)
Soft tissues	0	0.02	0.00	(0.00 - 216.98)	-0.25	(-0.25 - 54.85)
Mammary gland	2	0.62	3.24	(0.31 - 11.93)	19.45	(-6.02 - 94.72)
Cervix	0	0.04	0.00	(0.00 - 108.40)	-0.51	(-0.51 - 54.60)
Uterine body	0	0.15	0.00	(0.00 - 25.57)	-2.16	(-2.16 - 52.95)
Ovary	0	0.09	0.00	(0.00 - 43.93)	-1.25	(-1.25 - 53.85)
Kidney	1	0.05	19.05	(0.01 - 109.23)	13.32	(-0.73 - 79.84)
Urinary bladder	0	0.13	0.00	(0.00 - 30.23)	-1.82	(-1.82 - 53.29)
Pelvis, ureter and pathways	0	0.02	0.00	(0.00 - 247.79)	-0.22	(-0.22 - 54.89)
Urinary tract	0	0.15	0.00	(0.00 - 26.95)	-2.05	(-2.05 - 53.06)
Encephalon and CNS	0	0.04	0.00	(0.00 - 93.20)	-0.59	(-0.59 - 54.52)
Thyroid	0	0.02	0.00	(0.00 - 186.72)	-0.30	(-0.30 - 54.81)
Hodgkin Lymphoma	0	0.01	0.00	(0.00 - 505.49)	-0.11	(-0.11 - 55.00)
Non-Hodgkin Lymphoma	0	0.08	0.00	(0.00 - 47.34)	-1.16	(-1.16 - 53.94)
Multiple myeloma	1	0.06	17.07	(0.01 - 97.86)	13.23	(-0.82 - 79.75)
Leukaemia	0	0.10	0.00	(0.00 - 38.42)	-1.43	(-1.43 - 53.67)
Another	2	0.41	4.83	(0.46 - 17.75)	22.29	(-3.17 - 97.57)
All (excluding no melanoma skin tumours)	**10**	**3.08**	**3.24**	**(1.54 - 5.99) ***	**97.23**	**(23.61 - 216.17) ***

RISK OF A SMN AT MEN DIAGNOSED WITH PREVIOUS SALIVARY GLANDS CANCER

SECOND TUMORAL TYPE	OBS	ESP	SIR	SIR (CI 95%)	EAR	EAR (CI 95%)
Lip	2	0.03	75.15	(7.08 - 276.38) *	92.77	(7.61 - 344.51) *
Oral cavity	0	0.02	0.00	(0.00 - 260.25)	-0.71	(-0.71 - 183.58)
Salivary glands	0	0.00	0.00	(0.00 - 976.30)	-0.19	(-0.19 - 184.10)
Oropharynx	0	0.01	0.00	(0.00 - 486.06)	-0.38	(-0.38 - 183.91)
Nasopharynx	0	0.00	0.00	(0.00 - 999.99)	-0.08	(-0.08 - 184.22)
Hypopharynx	1	0.01	142.32	(0.06 - 815.80)	46.68	(-0.31 - 269.14)
Nasal cavities and sinus	0	0.00	0.00	(0.00 - 999.99)	-0.17	(-0.17 - 184.13)
Larynx	1	0.03	29.82	(0.01 - 170.96)	45.43	(-1.56 - 267.89)
Head and neck	**4**	**0.10**	**40.20**	**(10.46 - 103.96) ***	**183.36**	**(44.23 - 481.54) ***
Oesophagus	0	0.02	0.00	(0.00 - 157.09)	-1.17	(-1.17 - 183.12)
Stomach	0	0.11	0.00	(0.00 - 34.48)	-5.34	(-5.34 - 178.95)
Colon	1	0.29	3.49	(0.00 - 20.02)	33.55	(-13.44 - 256.01)
Rectum	0	0.11	0.00	(0.00 - 34.84)	-5.29	(-5.29 - 179.00)
Colon, rectum and anus	1	0.40	2.51	(0.00 - 14.37)	28.26	(-18.73 - 250.72)
Liver	0	0.07	0.00	(0.00 - 58.76)	-3.14	(-3.14 - 181.16)
Gallbladder and pathways	0	0.03	0.00	(0.00 - 123.54)	-1.49	(-1.49 - 182.80)
Pancreas	0	0.06	0.00	(0.00 - 70.31)	-2.62	(-2.62 - 181.67)
Lung	3	0.34	8.81	(1.66 - 26.07) *	125.01	(10.58 - 401.44) *
Bone and cartilage	0	0.00	0.00	(0.00 - 999.99)	-0.15	(-0.15 - 184.14)
Skin melanoma	0	0.03	0.00	(0.00 - 131.51)	-1.40	(-1.40 - 182.89)
Soft tissues	0	0.01	0.00	(0.00 - 378.71)	-0.49	(-0.49 - 183.81)
Prostate	1	0.60	1.66	(0.00 - 9.49)	18.63	(-28.36 - 241.08)
Testicle	0	0.00	0.00	(0.00 - 999.99)	-0.07	(-0.07 - 184.22)
Kidney	0	0.05	0.00	(0.00 - 72.94)	-2.53	(-2.53 - 181.77)
Urinary bladder	0	0.31	0.00	(0.00 - 12.68)	-14.53	(-14.53 - 169.76)
Pelvis, ureter and pathways	0	0.01	0.00	(0.00 - 296.75)	-0.62	(-0.62 - 183.67)
Urinary tract	0	0.32	0.00	(0.00 - 12.16)	-15.15	(-15.15 - 169.14)
Encephalon and CNS	0	0.03	0.00	(0.00 - 148.30)	-1.24	(-1.24 - 183.05)
Thyroid	0	0.00	0.00	(0.00 - 999.99)	-0.11	(-0.11 - 184.19)
Hodgkin Lymphoma	0	0.00	0.00	(0.00 - 999.99)	-0.16	(-0.16 - 184.13)
Non-Hodgkin Lymphoma	0	0.05	0.00	(0.00 - 79.10)	-2.33	(-2.33 - 181.96)
Multiple myeloma	0	0.03	0.00	(0.00 - 134.92)	-1.37	(-1.37 - 182.93)
Leukaemia	0	0.07	0.00	(0.00 - 56.25)	-3.28	(-3.28 - 181.02)
Another	0	0.22	0.00	(0.00 - 18.11)	-10.18	(-10.18 - 174.12)
All (excluding no melanoma skin tumours)	**9**	**2.56**	**3.52**	**(1.59 - 6.70) ***	**302.74**	**(71.48 - 686.26) ***

RISK OF A SMN AT WOMEN DIAGNOSED WITH PREVIOUS SALIVARY GLANDS CANCER

SECOND TUMORAL TYPE	OBS	ESP	SIR	SIR (CI 95%)	EAR	EAR (CI 95%)
Lip	0	0.01	0.00	(0.00 - 622.25)	-0.17	(-0.17 - 106.70)
Oral cavity	0	0.01	0.00	(0.00 - 296.93)	-0.36	(-0.36 - 106.51)
Salivary glands	0	0.00	0.00	(0.00 - 933.47)	-0.11	(-0.11 - 106.75)
Oropharynx	0	0.00	0.00	(0.00 - 999.99)	-0.06	(-0.06 - 106.80)
Nasopharynx	0	0.00	0.00	(0.00 - 999.99)	-0.02	(-0.02 - 106.85)
Hypopharynx	0	0.00	0.00	(0.00 - 999.99)	-0.01	(-0.01 - 106.86)
Nasal cavities and sinus	0	0.00	0.00	(0.00 - 999.99)	-0.09	(-0.09 - 106.78)
Larynx	0	0.00	0.00	(0.00 - 999.99)	-0.03	(-0.03 - 106.83)
Head and neck	**0**	**0.03**	**0.00**	**(0.00 - 124.07)**	**-0.86**	**(-0.86 - 106.01)**
Oesophagus	0	0.01	0.00	(0.00 - 516.26)	-0.21	(-0.21 - 106.66)
Stomach	0	0.10	0.00	(0.00 - 41.25)	-2.59	(-2.59 - 104.28)
Colon	1	0.23	4.43	(0.00 - 25.40)	21.11	(-6.14 - 150.11)
Rectum	0	0.08	0.00	(0.00 - 47.69)	-2.24	(-2.24 - 104.63)
Colon, rectum and anus	1	0.31	3.25	(0.00 - 18.62)	18.87	(-8.38 - 147.86)
Liver	0	0.04	0.00	(0.00 - 102.69)	-1.04	(-1.04 - 105.83)
Gallbladder and pathways	0	0.04	0.00	(0.00 - 99.50)	-1.07	(-1.07 - 105.79)
Pancreas	0	0.06	0.00	(0.00 - 63.15)	-1.69	(-1.69 - 105.18)
Lung	0	0.06	0.00	(0.00 - 70.79)	-1.51	(-1.51 - 105.36)
Bone and cartilage	0	0.00	0.00	(0.00 - 999.99)	-0.07	(-0.07 - 106.80)
Skin melanoma	0	0.03	0.00	(0.00 - 117.78)	-0.91	(-0.91 - 105.96)
Soft tissues	0	0.01	0.00	(0.00 - 389.82)	-0.27	(-0.27 - 106.59)
Mammary gland	3	0.36	8.28	(1.56 - 24.51) *	71.90	(5.54 - 232.20) *
Cervix	0	0.02	0.00	(0.00 - 179.44)	-0.60	(-0.60 - 106.27)
Uterine body	0	0.09	0.00	(0.00 - 45.33)	-2.36	(-2.36 - 104.51)
Ovary	0	0.05	0.00	(0.00 - 79.31)	-1.35	(-1.35 - 105.52)
Kidney	0	0.03	0.00	(0.00 - 133.22)	-0.80	(-0.80 - 106.07)
Urinary bladder	0	0.07	0.00	(0.00 - 57.15)	-1.87	(-1.87 - 105.00)
Pelvis, ureter and pathways	0	0.01	0.00	(0.00 - 479.59)	-0.22	(-0.22 - 106.65)
Urinary tract	0	0.08	0.00	(0.00 - 51.06)	-2.09	(-2.09 - 104.78)
Encephalon and CNS	0	0.02	0.00	(0.00 - 161.94)	-0.66	(-0.66 - 106.21)
Thyroid	1	0.01	71.70	(0.03 - 411.01)	26.88	(-0.37 - 155.88)
Hodgkin Lymphoma	0	0.00	0.00	(0.00 - 809.60)	-0.13	(-0.13 - 106.74)
Non-Hodgkin Lymphoma	0	0.05	0.00	(0.00 - 83.51)	-1.28	(-1.28 - 105.59)
Multiple myeloma	0	0.03	0.00	(0.00 - 119.33)	-0.90	(-0.90 - 105.97)
Leukaemia	0	0.06	0.00	(0.00 - 67.99)	-1.57	(-1.57 - 105.30)
Another	0	0.22	0.00	(0.00 - 18.11)	-5.90	(-5.90 - 100.97)
All (excluding no melanoma skin tumours)	**5**	**1.71**	**2.93**	**(0.92 - 6.89)**	**89.79**	**(-3.50 - 274.10)**

RISK OF A SMN AT MEN DIAGNOSED WITH PREVIOUS NASOPHARYNX CANCER

SECOND TUMORAL TYPE	OBS	ESP	SIR	SIR (CI 95%)	EAR	EAR (CI 95%)
Lip	0	0.07	0.00	(0.00 - 55.37)	-1.60	(-1.60 - 87.01)
Oral cavity	0	0.05	0.00	(0.00 - 78.21)	-1.13	(-1.13 - 87.47)
Salivary glands	0	0.01	0.00	(0.00 - 352.31)	-0.25	(-0.25 - 88.36)
Oropharynx	0	0.04	0.00	(0.00 - 111.31)	-0.80	(-0.80 - 87.81)
Nasopharynx	0	0.01	0.00	(0.00 - 571.09)	-0.16	(-0.16 - 88.45)
Hypopharynx	0	0.03	0.00	(0.00 - 136.51)	-0.65	(-0.65 - 87.96)
Nasal cavities and sinus	0	0.01	0.00	(0.00 - 401.34)	-0.22	(-0.22 - 88.39)
Larynx	0	0.12	0.00	(0.00 - 32.97)	-2.69	(-2.69 - 85.92)
Head and neck	**0**	**0.33**	**0.00**	**(0.00 - 11.82)**	**-7.49**	**(-7.49 - 81.11)**
Oesophagus	1	0.09	11.30	(0.00 - 64.78)	20.60	(-1.99 - 127.56)
Stomach	0	0.30	0.00	(0.00 - 13.23)	-6.70	(-6.70 - 81.91)
Colon	0	0.75	0.00	(0.00 - 5.25)	-16.87	(-16.87 - 71.74)
Rectum	0	0.33	0.00	(0.00 - 12.01)	-7.38	(-7.38 - 81.23)
Colon, rectum and anus	0	1.07	0.00	(0.00 - 3.65)	-24.25	(-24.25 - 64.36)
Liver	0	0.18	0.00	(0.00 - 21.20)	-4.18	(-4.18 - 84.43)
Gallbladder and pathways	0	0.07	0.00	(0.00 - 55.99)	-1.58	(-1.58 - 87.02)
Pancreas	0	0.16	0.00	(0.00 - 24.22)	-3.66	(-3.66 - 84.95)
Lung	1	1.01	0.99	(0.00 - 5.69)	-0.18	(-22.77 - 106.78)
Bone and cartilage	0	0.01	0.00	(0.00 - 453.48)	-0.20	(-0.20 - 88.41)
Skin melanoma	0	0.08	0.00	(0.00 - 47.93)	-1.85	(-1.85 - 86.76)
Soft tissues	0	0.03	0.00	(0.00 - 117.90)	-0.75	(-0.75 - 87.86)
Prostate	2	1.64	1.22	(0.12 - 4.49)	8.18	(-32.76 - 129.22)
Testicle	0	0.01	0.00	(0.00 - 511.01)	-0.17	(-0.17 - 88.43)
Kidney	1	0.15	6.83	(0.00 - 39.15)	19.29	(-3.30 - 126.25)
Urinary bladder	0	0.81	0.00	(0.00 - 4.86)	-18.25	(-18.25 - 70.36)
Pelvis, ureter and pathways	0	0.04	0.00	(0.00 - 107.56)	-0.82	(-0.82 - 87.78)
Urinary tract	0	0.84	0.00	(0.00 - 4.65)	-19.07	(-19.07 - 69.53)
Encephalon and CNS	0	0.07	0.00	(0.00 - 57.80)	-1.53	(-1.53 - 87.07)
Thyroid	0	0.01	0.00	(0.00 - 360.88)	-0.25	(-0.25 - 88.36)
Hodgkin Lymphoma	0	0.01	0.00	(0.00 - 309.59)	-0.29	(-0.29 - 88.32)
Non-Hodgkin Lymphoma	0	0.16	0.00	(0.00 - 25.07)	-3.53	(-3.53 - 85.07)
Multiple myeloma	0	0.09	0.00	(0.00 - 43.96)	-2.02	(-2.02 - 86.59)
Leukaemia	0	0.19	0.00	(0.00 - 20.78)	-4.26	(-4.26 - 84.34)
Another	0	0.54	0.00	(0.00 - 7.25)	-12.22	(-12.22 - 76.39)
All (excluding no melanoma skin tumours)	**5**	**7.05**	**0.71**	**(0.22 - 1.67)**	**-46.41**	**(-123.76 - 106.40)**

RISK OF A SMN AT WOMEN DIAGNOSED WITH PREVIOUS NASOPHARYNX CANCER

SECOND TUMORAL TYPE	OBS	ESP	SIR	SIR (CI 95%)	EAR	EAR (CI 95%)
Lip	0	0.00	0.00	(0.00 - 999.99)	-0.30	(-0.30 - 362.56)
Oral cavity	0	0.01	0.00	(0.00 - 628.75)	-0.58	(-0.58 - 362.28)
Salivary glands	0	0.00	0.00	(0.00 - 999.99)	-0.18	(-0.18 - 362.69)
Oropharynx	0	0.00	0.00	(0.00 - 999.99)	-0.14	(-0.14 - 362.72)
Nasopharynx	0	0.00	0.00	(0.00 - 999.99)	-0.04	(-0.04 - 362.83)
Hypopharynx	0	0.00	0.00	(0.00 - 999.99)	-0.01	(-0.01 - 362.85)
Nasal cavities and sinus	0	0.00	0.00	(0.00 - 999.99)	-0.10	(-0.10 - 362.76)
Larynx	0	0.00	0.00	(0.00 - 999.99)	-0.06	(-0.06 - 362.80)
Head and neck	**0**	**0.02**	**0.00**	**(0.00 - 257.84)**	**-1.41**	**(-1.41 - 361.45)**
Oesophagus	0	0.00	0.00	(0.00 - 999.99)	-0.30	(-0.30 - 362.57)
Stomach	0	0.04	0.00	(0.00 - 91.86)	-3.95	(-3.95 - 358.91)
Colon	0	0.11	0.00	(0.00 - 35.83)	-10.13	(-10.13 - 352.74)
Rectum	0	0.04	0.00	(0.00 - 94.21)	-3.85	(-3.85 - 359.01)
Colon, rectum and anus	0	0.15	0.00	(0.00 - 25.96)	-13.98	(-13.98 - 348.88)
Liver	0	0.02	0.00	(0.00 - 221.93)	-1.64	(-1.64 - 361.23)
Gallbladder and pathways	0	0.02	0.00	(0.00 - 216.40)	-1.68	(-1.68 - 361.19)
Pancreas	0	0.03	0.00	(0.00 - 137.43)	-2.64	(-2.64 - 360.22)
Lung	0	0.03	0.00	(0.00 - 132.47)	-2.74	(-2.74 - 360.12)
Bone and cartilage	0	0.00	0.00	(0.00 - 999.99)	-0.10	(-0.10 - 362.76)
Skin melanoma	0	0.02	0.00	(0.00 - 254.83)	-1.42	(-1.42 - 361.44)
Soft tissues	0	0.00	0.00	(0.00 - 847.92)	-0.43	(-0.43 - 362.43)
Mammary gland	2	0.18	10.90	(1.03 - 40.07) *	168.12	(0.46 - 663.79) *
Cervix	0	0.01	0.00	(0.00 - 352.02)	-1.03	(-1.03 - 361.83)
Uterine body	0	0.04	0.00	(0.00 - 87.15)	-4.16	(-4.16 - 358.70)
Ovary	0	0.03	0.00	(0.00 - 149.46)	-2.43	(-2.43 - 360.43)
Kidney	0	0.02	0.00	(0.00 - 260.40)	-1.39	(-1.39 - 361.47)
Urinary bladder	0	0.03	0.00	(0.00 - 119.79)	-3.03	(-3.03 - 359.83)
Pelvis, ureter and pathways	0	0.00	0.00	(0.00 - 999.99)	-0.34	(-0.34 - 362.53)
Urinary tract	0	0.04	0.00	(0.00 - 107.82)	-3.37	(-3.37 - 359.50)
Encephalon and CNS	0	0.01	0.00	(0.00 - 304.76)	-1.19	(-1.19 - 361.67)
Thyroid	1	0.01	149.17	(0.06 - 855.07)	91.94	(-0.58 - 529.94)
Hodgkin Lymphoma	0	0.00	0.00	(0.00 - 999.99)	-0.19	(-0.19 - 362.67)
Non-Hodgkin Lymphoma	0	0.02	0.00	(0.00 - 165.85)	-2.19	(-2.19 - 360.67)
Multiple myeloma	0	0.02	0.00	(0.00 - 247.03)	-1.47	(-1.47 - 361.39)
Leukaemia	0	0.03	0.00	(0.00 - 154.21)	-2.35	(-2.35 - 360.51)
Another	0	0.10	0.00	(0.00 - 40.94)	-8.86	(-8.86 - 354.00)
All (excluding no melanoma skin tumours)	**3**	**0.83**	**3.63**	**(0.68 - 10.74)**	**201.15**	**(-24.17 - 745.42)**

RISK OF A SMN AT MEN DIAGNOSED WITH PREVIOUS OROPHARYNX CANCER

SECOND TUMORAL TYPE	OBS	ESP	SIR	SIR (CI 95%)	EAR	EAR (CI 95%)
Lip	0	0.09	0.00	(0.00 - 41.42)	-1.70	(-1.70 - 68.88)
Oral cavity	2	0.07	30.35	(2.86 - 111.62) *	34.82	(2.21 - 131.23) *
Salivary glands	0	0.02	0.00	(0.00 - 240.13)	-0.29	(-0.29 - 70.29)
Oropharynx	0	0.04	0.00	(0.00 - 91.97)	-0.77	(-0.77 - 69.81)
Nasopharynx	0	0.01	0.00	(0.00 - 564.54)	-0.13	(-0.13 - 70.46)
Hypopharynx	1	0.03	32.75	(0.01 - 187.74)	17.45	(-0.54 - 102.65)
Nasal cavities and sinus	0	0.01	0.00	(0.00 - 356.91)	-0.20	(-0.20 - 70.38)
Larynx	4	0.14	29.26	(7.61 - 75.67) *	69.55	(16.27 - 183.75) *
Head and neck	**7**	**0.40**	**17.30**	**(6.86 - 35.85) ***	**118.74**	**(42.67 - 253.84) ***
Oesophagus	5	0.11	46.96	(14.82 - 110.46) *	88.10	(26.49 - 209.83) *
Stomach	0	0.40	0.00	(0.00 - 9.76)	-7.23	(-7.23 - 63.35)
Colon	2	0.96	2.09	(0.20 - 7.67)	18.74	(-13.87 - 115.16)
Rectum	2	0.42	4.75	(0.45 - 17.47)	28.43	(-4.19 - 124.84)
Colon, rectum and anus	4	1.38	2.90	(0.75 - 7.49)	47.17	(-6.11 - 161.37)
Liver	0	0.23	0.00	(0.00 - 16.71)	-4.23	(-4.23 - 66.36)
Gallbladder and pathways	0	0.10	0.00	(0.00 - 39.04)	-1.81	(-1.81 - 68.77)
Pancreas	0	0.20	0.00	(0.00 - 20.03)	-3.52	(-3.52 - 67.06)
Lung	15	1.28	11.71	(6.53 - 19.36) *	247.00	(127.62 - 423.44) *
Bone and cartilage	0	0.01	0.00	(0.00 - 468.26)	-0.15	(-0.15 - 70.43)
Skin melanoma	0	0.10	0.00	(0.00 - 38.07)	-1.85	(-1.85 - 68.73)
Soft tissues	0	0.04	0.00	(0.00 - 105.93)	-0.67	(-0.67 - 69.92)
Prostate	2	2.19	0.91	(0.09 - 3.36)	-3.44	(-36.05 - 92.98)
Testicle	0	0.01	0.00	(0.00 - 654.35)	-0.11	(-0.11 - 70.47)
Kidney	0	0.18	0.00	(0.00 - 21.63)	-3.26	(-3.26 - 67.32)
Urinary bladder	1	1.08	0.93	(0.00 - 5.31)	-1.42	(-19.42 - 83.78)
Pelvis, ureter and pathways	0	0.05	0.00	(0.00 - 82.58)	-0.85	(-0.85 - 69.73)
Urinary tract	1	1.13	0.89	(0.00 - 5.09)	-2.28	(-20.27 - 82.92)
Encephalon and CNS	0	0.09	0.00	(0.00 - 42.75)	-1.65	(-1.65 - 68.93)
Thyroid	1	0.01	72.87	(0.03 - 417.72)	17.76	(-0.24 - 102.95)
Hodgkin Lymphoma	0	0.01	0.00	(0.00 - 309.36)	-0.23	(-0.23 - 70.35)
Non-Hodgkin Lymphoma	0	0.18	0.00	(0.00 - 21.23)	-3.32	(-3.32 - 67.26)
Multiple myeloma	0	0.10	0.00	(0.00 - 37.34)	-1.89	(-1.89 - 68.69)
Leukaemia	0	0.24	0.00	(0.00 - 16.16)	-4.37	(-4.37 - 66.21)
Another	0	0.70	0.00	(0.00 - 5.57)	-12.66	(-12.66 - 57.92)
All (excluding no melanoma skin tumours)	**35**	**9.13**	**3.83**	**(2.67 - 5.33) ***	**465.70**	**(274.23 - 712.72) ***

RISK OF A SMN AT WOMEN DIAGNOSED WITH PREVIOUS OROPHARYNX CANCER

SECOND TUMORAL TYPE	OBS	ESP	SIR	SIR (CI 95%)	EAR	EAR (CI 95%)
Lip	0	0.00	0.00	(0.00 - 999.99)	-0.35	(-0.35 - 422.60)
Oral cavity	0	0.01	0.00	(0.00 - 560.21)	-0.75	(-0.75 - 422.19)
Salivary glands	0	0.00	0.00	(0.00 - 999.99)	-0.27	(-0.27 - 422.67)
Oropharynx	0	0.00	0.00	(0.00 - 999.99)	-0.09	(-0.09 - 422.86)
Nasopharynx	0	0.00	0.00	(0.00 - 999.99)	-0.01	(-0.01 - 422.93)
Hypopharynx	0	0.00	Nan	(0.00 - 999.99)	0.00	(0.00 - 422.95)
Nasal cavities and sinus	0	0.00	0.00	(0.00 - 999.99)	-0.15	(-0.15 - 422.80)
Larynx	0	0.00	0.00	(0.00 - 999.99)	-0.06	(-0.06 - 422.89)
Head and neck	**0**	**0.02**	**0.00**	**(0.00 - 251.68)**	**-1.68**	**(-1.68 - 421.27)**
Oesophagus	1	0.00	303.51	(0.12 - 999.99)	107.53	(-0.31 - 618.06)
Stomach	0	0.05	0.00	(0.00 - 79.55)	-5.32	(-5.32 - 417.63)
Colon	1	0.11	8.81	(0.00 - 50.52)	95.64	(-12.20 - 606.17)
Rectum	0	0.04	0.00	(0.00 - 99.67)	-4.24	(-4.24 - 418.70)
Colon, rectum and anus	1	0.15	6.54	(0.00 - 37.51)	91.40	(-16.44 - 601.93)
Liver	0	0.02	0.00	(0.00 - 210.45)	-2.01	(-2.01 - 420.94)
Gallbladder and pathways	0	0.02	0.00	(0.00 - 203.59)	-2.08	(-2.08 - 420.87)
Pancreas	0	0.03	0.00	(0.00 - 119.19)	-3.55	(-3.55 - 419.40)
Lung	0	0.03	0.00	(0.00 - 148.24)	-2.85	(-2.85 - 420.09)
Bone and cartilage	0	0.00	0.00	(0.00 - 999.99)	-0.11	(-0.11 - 422.84)
Skin melanoma	0	0.02	0.00	(0.00 - 246.84)	-1.71	(-1.71 - 421.23)
Soft tissues	0	0.01	0.00	(0.00 - 764.67)	-0.55	(-0.55 - 422.39)
Mammary gland	0	0.16	0.00	(0.00 - 24.57)	-17.21	(-17.21 - 405.73)
Cervix	1	0.01	110.37	(0.04 - 632.68)	106.91	(-0.93 - 617.44)
Uterine body	0	0.04	0.00	(0.00 - 89.64)	-4.72	(-4.72 - 418.23)
Ovary	0	0.02	0.00	(0.00 - 180.95)	-2.34	(-2.34 - 420.61)
Kidney	0	0.02	0.00	(0.00 - 243.85)	-1.73	(-1.73 - 421.21)
Urinary bladder	0	0.03	0.00	(0.00 - 113.62)	-3.72	(-3.72 - 419.22)
Pelvis, ureter and pathways	0	0.00	0.00	(0.00 - 875.84)	-0.48	(-0.48 - 422.46)
Urinary tract	0	0.04	0.00	(0.00 - 100.58)	-4.21	(-4.21 - 418.74)
Encephalon and CNS	0	0.01	0.00	(0.00 - 323.19)	-1.31	(-1.31 - 421.64)
Thyroid	0	0.00	0.00	(0.00 - 848.50)	-0.50	(-0.50 - 422.45)
Hodgkin Lymphoma	0	0.00	0.00	(0.00 - 999.99)	-0.18	(-0.18 - 422.77)
Non-Hodgkin Lymphoma	0	0.02	0.00	(0.00 - 182.73)	-2.31	(-2.31 - 420.63)
Multiple myeloma	0	0.02	0.00	(0.00 - 222.58)	-1.90	(-1.90 - 421.05)
Leukaemia	0	0.03	0.00	(0.00 - 142.37)	-2.97	(-2.97 - 419.98)
Another	0	0.11	0.00	(0.00 - 35.44)	-11.93	(-11.93 - 411.01)
All (excluding no melanoma skin tumours)	**3**	**0.82**	**3.64**	**(0.69 - 10.77)**	**234.66**	**(-27.97 - 869.06)**

RISK OF A SMN AT MEN DIAGNOSED WITH PREVIOUS HYPOPHARYNX CANCER

SECOND TUMORAL TYPE	OBS	ESP	SIR	SIR (CI 95%)	EAR	EAR (CI 95%)
Lip	1	0.11	8.70	(0.00 - 49.85)	12.81	(-1.66 - 81.33)
Oral cavity	0	0.07	0.00	(0.00 - 57.52)	-0.99	(-0.99 - 55.77)
Salivary glands	0	0.02	0.00	(0.00 - 168.52)	-0.34	(-0.34 - 56.42)
Oropharynx	0	0.04	0.00	(0.00 - 93.33)	-0.61	(-0.61 - 56.15)
Nasopharynx	0	0.01	0.00	(0.00 - 701.69)	-0.08	(-0.08 - 56.68)
Hypopharynx	0	0.03	0.00	(0.00 - 142.54)	-0.40	(-0.40 - 56.36)
Nasal cavities and sinus	0	0.01	0.00	(0.00 - 314.32)	-0.18	(-0.18 - 56.58)
Larynx	0	0.15	0.00	(0.00 - 26.22)	-2.16	(-2.16 - 54.60)
Head and neck	**1**	**0.44**	**2.25**	**(0.00 - 12.93)**	**8.06**	**(-6.41 - 76.57)**
Oesophagus	5	0.11	43.67	(13.78 - 102.72) *	70.73	(21.18 - 168.62) *
Stomach	1	0.47	2.11	(0.00 - 12.11)	7.62	(-6.85 - 76.14)
Colon	5	1.18	4.24	(1.34 - 9.97) *	55.30	(5.76 - 153.20) *
Rectum	0	0.49	0.00	(0.00 - 7.95)	-7.14	(-7.14 - 49.62)
Colon, rectum and anus	5	1.67	2.99	(0.94 - 7.03)	48.16	(-1.39 - 146.05)
Liver	1	0.27	3.70	(0.00 - 21.24)	10.57	(-3.90 - 79.08)
Gallbladder and pathways	0	0.12	0.00	(0.00 - 34.01)	-1.67	(-1.67 - 55.09)
Pancreas	0	0.26	0.00	(0.00 - 15.32)	-3.70	(-3.70 - 53.06)
Lung	20	1.45	13.76	(8.39 - 21.29) *	268.52	(155.52 - 426.95) *
Bone and cartilage	0	0.01	0.00	(0.00 - 312.85)	-0.18	(-0.18 - 56.58)
Skin melanoma	1	0.12	8.10	(0.00 - 46.41)	12.69	(-1.78 - 81.20)
Soft tissues	0	0.05	0.00	(0.00 - 80.24)	-0.71	(-0.71 - 56.05)
Prostate	2	2.60	0.77	(0.07 - 2.83)	-8.68	(-34.91 - 68.85)
Testicle	0	0.01	0.00	(0.00 - 566.60)	-0.10	(-0.10 - 56.66)
Kidney	1	0.22	4.63	(0.00 - 26.51)	11.35	(-3.12 - 79.86)
Urinary bladder	2	1.26	1.58	(0.15 - 5.82)	10.65	(-15.58 - 88.18)
Pelvis, ureter and pathways	0	0.06	0.00	(0.00 - 66.56)	-0.85	(-0.85 - 55.91)
Urinary tract	2	1.32	1.51	(0.14 - 5.56)	9.79	(-16.43 - 87.33)
Encephalon and CNS	0	0.10	0.00	(0.00 - 38.11)	-1.49	(-1.49 - 55.27)
Thyroid	0	0.01	0.00	(0.00 - 294.05)	-0.19	(-0.19 - 56.57)
Hodgkin Lymphoma	0	0.02	0.00	(0.00 - 229.12)	-0.25	(-0.25 - 56.51)
Non-Hodgkin Lymphoma	0	0.23	0.00	(0.00 - 17.05)	-3.33	(-3.33 - 53.43)
Multiple myeloma	0	0.13	0.00	(0.00 - 29.11)	-1.95	(-1.95 - 54.81)
Leukaemia	0	0.30	0.00	(0.00 - 13.18)	-4.31	(-4.31 - 52.45)
Another	1	0.86	1.16	(0.00 - 6.64)	1.99	(-12.49 - 70.50)
All (excluding no melanoma skin tumours)	**40**	**10.81**	**3.70**	**(2.64 - 5.04) ***	**422.58**	**(257.01 - 632.66) ***

RISK OF A SMN AT WOMEN DIAGNOSED WITH PREVIOUS HYPOPHARYNX CANCER

SECOND TUMORAL TYPE	OBS	ESP	SIR	SIR (CI 95%)	EAR	EAR (CI 95%)
Lip	0	0.00	0.00	(0.00 - 999.99)	-0.22	(-0.22 - 764.15)
Oral cavity	0	0.00	0.00	(0.00 - 999.99)	-0.49	(-0.49 - 763.88)
Salivary glands	0	0.00	0.00	(0.00 - 999.99)	-0.11	(-0.11 - 764.26)
Oropharynx	0	0.00	0.00	(0.00 - 999.99)	-0.07	(-0.07 - 764.30)
Nasopharynx	0	0.00	0.00	(0.00 - 999.99)	-0.02	(-0.02 - 764.35)
Hypopharynx	0	0.00	0.00	(0.00 - 999.99)	-0.02	(-0.02 - 764.35)
Nasal cavities and sinus	0	0.00	0.00	(0.00 - 999.99)	-0.05	(-0.05 - 764.32)
Larynx	0	0.00	0.00	(0.00 - 999.99)	-0.06	(-0.06 - 764.31)
Head and neck	**0**	**0.01**	**0.00**	**(0.00 - 742.89)**	**-1.03**	**(-1.03 - 763.34)**
Oesophagus	2	0.00	1395.91	(131.59 - 999.99) *	389.66	(36.48 - 1433.78) *
Stomach	0	0.02	0.00	(0.00 - 191.31)	-4.00	(-4.00 - 760.37)
Colon	0	0.04	0.00	(0.00 - 89.04)	-8.58	(-8.58 - 755.78)
Rectum	0	0.02	0.00	(0.00 - 203.24)	-3.76	(-3.76 - 760.61)
Colon, rectum and anus	0	0.06	0.00	(0.00 - 61.92)	-12.35	(-12.35 - 752.02)
Liver	0	0.01	0.00	(0.00 - 506.38)	-1.51	(-1.51 - 762.86)
Gallbladder and pathways	0	0.01	0.00	(0.00 - 507.46)	-1.51	(-1.51 - 762.86)
Pancreas	0	0.01	0.00	(0.00 - 337.17)	-2.27	(-2.27 - 762.10)
Lung	0	0.01	0.00	(0.00 - 402.35)	-1.90	(-1.90 - 762.47)
Bone and cartilage	0	0.00	0.00	(0.00 - 999.99)	-0.08	(-0.08 - 764.28)
Skin melanoma	0	0.01	0.00	(0.00 - 608.56)	-1.26	(-1.26 - 763.11)
Soft tissues	0	0.00	0.00	(0.00 - 999.99)	-0.31	(-0.31 - 764.05)
Mammary gland	0	0.06	0.00	(0.00 - 61.50)	-12.43	(-12.43 - 751.94)
Cervix	0	0.00	0.00	(0.00 - 999.99)	-0.76	(-0.76 - 763.60)
Uterine body	0	0.02	0.00	(0.00 - 235.17)	-3.25	(-3.25 - 761.12)
Ovary	0	0.01	0.00	(0.00 - 324.83)	-2.35	(-2.35 - 762.01)
Kidney	0	0.00	0.00	(0.00 - 880.26)	-0.87	(-0.87 - 763.50)
Urinary bladder	0	0.01	0.00	(0.00 - 299.88)	-2.55	(-2.55 - 761.82)
Pelvis, ureter and pathways	0	0.00	0.00	(0.00 - 999.99)	-0.52	(-0.52 - 763.84)
Urinary tract	0	0.02	0.00	(0.00 - 248.85)	-3.07	(-3.07 - 761.29)
Encephalon and CNS	0	0.00	0.00	(0.00 - 999.99)	-0.69	(-0.69 - 763.68)
Thyroid	0	0.00	0.00	(0.00 - 999.99)	-0.35	(-0.35 - 764.02)
Hodgkin Lymphoma	0	0.00	0.00	(0.00 - 999.99)	-0.16	(-0.16 - 764.21)
Non-Hodgkin Lymphoma	0	0.01	0.00	(0.00 - 376.25)	-2.03	(-2.03 - 762.34)
Multiple myeloma	0	0.01	0.00	(0.00 - 689.90)	-1.11	(-1.11 - 763.26)
Leukaemia	0	0.01	0.00	(0.00 - 373.07)	-2.05	(-2.05 - 762.32)
Another	0	0.04	0.00	(0.00 - 93.64)	-8.16	(-8.16 - 756.20)
All (excluding no melanoma skin tumours)	**2**	**0.33**	**6.12**	**(0.58 - 22.49)**	**326.18**	**(-27.01 - 1370.29)**

RISK OF A SMN AT MEN DIAGNOSED WITH PREVIOUS NASAL CAVITY OR SINUS CANCER

SECOND TUMORAL TYPE	OBS	ESP	SIR	SIR (CI 95%)	EAR	EAR (CI 95%)
Lip	0	0.02	0.00	(0.00 - 196.10)	-0.99	(-0.99 - 193.59)
Oral cavity	1	0.01	80.90	(0.03 - 463.76)	49.02	(-0.59 - 283.90)
Salivary glands	0	0.00	0.00	(0.00 - 999.99)	-0.16	(-0.16 - 194.43)
Oropharynx	0	0.01	0.00	(0.00 - 466.17)	-0.42	(-0.42 - 194.17)
Nasopharynx	0	0.00	0.00	(0.00 - 999.99)	-0.06	(-0.06 - 194.53)
Hypopharynx	0	0.01	0.00	(0.00 - 690.86)	-0.28	(-0.28 - 194.30)
Nasal cavities and sinus	0	0.00	0.00	(0.00 - 999.99)	-0.10	(-0.10 - 194.48)
Larynx	0	0.03	0.00	(0.00 - 131.24)	-1.48	(-1.48 - 193.10)
Head and neck	**1**	**0.08**	**12.09**	**(0.00 - 69.28)**	**45.53**	**(-4.09 - 280.41)**
Oesophagus	0	0.02	0.00	(0.00 - 157.52)	-1.24	(-1.24 - 193.35)
Stomach	0	0.09	0.00	(0.00 - 43.88)	-4.43	(-4.43 - 190.15)
Colon	0	0.22	0.00	(0.00 - 17.83)	-10.91	(-10.91 - 183.67)
Rectum	0	0.10	0.00	(0.00 - 40.91)	-4.76	(-4.76 - 189.83)
Colon, rectum and anus	0	0.32	0.00	(0.00 - 12.42)	-15.67	(-15.67 - 178.91)
Liver	0	0.05	0.00	(0.00 - 76.98)	-2.53	(-2.53 - 192.06)
Gallbladder and pathways	0	0.02	0.00	(0.00 - 181.72)	-1.07	(-1.07 - 193.51)
Pancreas	0	0.05	0.00	(0.00 - 85.69)	-2.27	(-2.27 - 192.31)
Lung	3	0.28	10.67	(2.01 - 31.58) *	134.95	(14.12 - 426.81) *
Bone and cartilage	0	0.00	0.00	(0.00 - 999.99)	-0.08	(-0.08 - 194.50)
Skin melanoma	0	0.02	0.00	(0.00 - 178.08)	-1.09	(-1.09 - 193.49)
Soft tissues	0	0.01	0.00	(0.00 - 408.53)	-0.48	(-0.48 - 194.11)
Prostate	2	0.47	4.27	(0.40 - 15.69)	76.00	(-13.91 - 341.80)
Testicle	0	0.00	0.00	(0.00 - 999.99)	-0.11	(-0.11 - 194.47)
Kidney	0	0.04	0.00	(0.00 - 97.59)	-1.99	(-1.99 - 192.59)
Urinary bladder	0	0.22	0.00	(0.00 - 17.68)	-11.01	(-11.01 - 183.58)
Pelvis, ureter and pathways	0	0.01	0.00	(0.00 - 349.13)	-0.56	(-0.56 - 194.03)
Urinary tract	0	0.23	0.00	(0.00 - 16.83)	-11.56	(-11.56 - 183.02)
Encephalon and CNS	0	0.02	0.00	(0.00 - 197.57)	-0.98	(-0.98 - 193.60)
Thyroid	0	0.00	0.00	(0.00 - 999.99)	-0.16	(-0.16 - 194.42)
Hodgkin Lymphoma	0	0.00	0.00	(0.00 - 872.25)	-0.22	(-0.22 - 194.36)
Non-Hodgkin Lymphoma	0	0.04	0.00	(0.00 - 96.40)	-2.02	(-2.02 - 192.57)
Multiple myeloma	0	0.03	0.00	(0.00 - 152.93)	-1.27	(-1.27 - 193.31)
Leukaemia	0	0.05	0.00	(0.00 - 72.86)	-2.67	(-2.67 - 191.91)
Another	0	0.16	0.00	(0.00 - 24.50)	-7.94	(-7.94 - 186.64)
All (excluding no melanoma skin tumours)	**6**	**2.00**	**3.00**	**(1.08 - 6.57) ***	**198.49**	**(7.87 - 553.18) ***

RISK OF A SMN AT WOMEN DIAGNOSED WITH PREVIOUS NASAL CAVITIES OR SINUS CANCER

SECOND TUMORAL TYPE	OBS	ESP	SIR	SIR (CI 95%)	EAR	EAR (CI 95%)
Lip	0	0.00	0.00	(0.00 - 999.99)	-0.08	(-0.08 - 388.17)
Oral cavity	0	0.00	0.00	(0.00 - 999.99)	-0.23	(-0.23 - 388.02)
Salivary glands	0	0.00	0.00	(0.00 - 999.99)	-0.08	(-0.08 - 388.17)
Oropharynx	0	0.00	0.00	(0.00 - 999.99)	-0.06	(-0.06 - 388.20)
Nasopharynx	0	0.00	0.00	(0.00 - 999.99)	-0.02	(-0.02 - 388.24)
Hypopharynx	0	0.00	0.00	(0.00 - 999.99)	-0.01	(-0.01 - 388.25)
Nasal cavities and sinus	0	0.00	0.00	(0.00 - 999.99)	-0.03	(-0.03 - 388.23)
Larynx	0	0.00	0.00	(0.00 - 999.99)	-0.05	(-0.05 - 388.20)
Head and neck	**0**	**0.01**	**0.00**	**(0.00 - 694.47)**	**-0.56**	**(-0.56 - 387.70)**
Oesophagus	0	0.00	0.00	(0.00 - 999.99)	-0.13	(-0.13 - 388.13)
Stomach	0	0.02	0.00	(0.00 - 235.72)	-1.65	(-1.65 - 386.61)
Colon	0	0.04	0.00	(0.00 - 101.35)	-3.83	(-3.83 - 384.43)
Rectum	1	0.02	60.69	(0.02 - 347.88)	97.40	(-1.59 - 566.06)
Colon, rectum and anus	1	0.06	18.13	(0.01 - 103.92)	93.57	(-5.42 - 562.23)
Liver	0	0.01	0.00	(0.00 - 697.39)	-0.56	(-0.56 - 387.70)
Gallbladder and pathways	0	0.01	0.00	(0.00 - 565.65)	-0.69	(-0.69 - 387.57)
Pancreas	0	0.01	0.00	(0.00 - 381.69)	-1.02	(-1.02 - 387.24)
Lung	0	0.01	0.00	(0.00 - 343.92)	-1.13	(-1.13 - 387.13)
Bone and cartilage	0	0.00	0.00	(0.00 - 999.99)	-0.05	(-0.05 - 388.20)
Skin melanoma	0	0.01	0.00	(0.00 - 615.07)	-0.63	(-0.63 - 387.62)
Soft tissues	0	0.00	0.00	(0.00 - 999.99)	-0.15	(-0.15 - 388.10)
Mammary gland	0	0.07	0.00	(0.00 - 53.97)	-7.19	(-7.19 - 381.06)
Cervix	0	0.00	0.00	(0.00 - 860.44)	-0.45	(-0.45 - 387.80)
Uterine body	0	0.02	0.00	(0.00 - 214.33)	-1.81	(-1.81 - 386.44)
Ovary	0	0.01	0.00	(0.00 - 364.09)	-1.07	(-1.07 - 387.19)
Kidney	0	0.00	0.00	(0.00 - 789.52)	-0.49	(-0.49 - 387.76)
Urinary bladder	0	0.01	0.00	(0.00 - 383.41)	-1.01	(-1.01 - 387.24)
Pelvis, ureter and pathways	0	0.00	0.00	(0.00 - 999.99)	-0.18	(-0.18 - 388.07)
Urinary tract	0	0.01	0.00	(0.00 - 324.77)	-1.20	(-1.20 - 387.06)
Encephalon and CNS	0	0.00	0.00	(0.00 - 854.78)	-0.45	(-0.45 - 387.80)
Thyroid	0	0.00	0.00	(0.00 - 999.99)	-0.29	(-0.29 - 387.96)
Hodgkin Lymphoma	0	0.00	0.00	(0.00 - 999.99)	-0.12	(-0.12 - 388.14)
Non-Hodgkin Lymphoma	0	0.01	0.00	(0.00 - 402.99)	-0.96	(-0.96 - 387.29)
Multiple myeloma	0	0.01	0.00	(0.00 - 598.37)	-0.65	(-0.65 - 387.61)
Leukaemia	0	0.01	0.00	(0.00 - 405.65)	-0.96	(-0.96 - 387.30)
Another	0	0.03	0.00	(0.00 - 117.04)	-3.32	(-3.32 - 384.94)
All (excluding no melanoma skin tumours)	**1**	**0.31**	**3.20**	**(0.00 - 18.32)**	**68.05**	**(-30.95 - 536.71)**

RISK OF A SMN AT MEN DIAGNOSED WITH PREVIOUS LARYNX CANCER

SECOND TUMORAL TYPE	OBS	ESP	SIR	SIR (CI 95%)	EAR	EAR (CI 95%)
Lip	1	0.53	1.88	(0.00 - 10.77)	1.18	(-1.34 - 13.13)
Oral cavity	3	0.31	9.64	(1.82 - 28.53) *	6.79	(0.64 - 21.64) *
Salivary glands	1	0.10	10.18	(0.00 - 58.33)	2.28	(-0.25 - 14.23)
Oropharynx	3	0.19	15.97	(3.01 - 47.27) *	7.10	(0.95 - 21.95) *
Nasopharynx	0	0.03	0.00	(0.00 - 146.71)	-0.07	(-0.07 - 9.83)
Hypopharynx	3	0.13	22.23	(4.19 - 65.79) *	7.23	(1.09 - 22.08) *
Nasal cavities and sinus	0	0.06	0.00	(0.00 - 62.96)	-0.16	(-0.16 - 9.74)
Larynx	0	0.69	0.00	(0.00 - 5.66)	-1.75	(-1.75 - 8.15)
Head and neck	**11**	**2.05**	**5.37**	**(2.67 - 9.65) ***	**22.61**	**(8.62 - 44.70) ***
Oesophagus	6	0.50	11.89	(4.28 - 26.05) *	13.88	(4.18 - 31.92) *
Stomach	4	2.25	1.78	(0.46 - 4.60)	4.42	(-3.05 - 20.44)
Colon	13	5.56	2.34	(1.24 - 4.01) *	18.77	(3.36 - 42.24) *
Rectum	3	2.26	1.33	(0.25 - 3.93)	1.88	(-4.27 – 16.72)
Colon, rectum and anus	16	7.82	2.05	(1.17 - 3.33) *	20.65	(3.28 - 46.00) *
Liver	3	1.27	2.36	(0.44 - 6.98)	4.36	(-1.78 - 19.21)
Gallbladder and pathways	1	0.55	1.80	(0.00 - 10.33)	1.12	(-1.40 - 13.07)
Pancreas	4	1.15	3.49	(0.91 - 9.03)	7.21	(-0.27 - 23.22)
Lung	60	6.76	8.88	(6.78 - 11.44) *	134.44	(98.53 - 178.04) *
Bone and cartilage	0	0.06	0.00	(0.00 - 67.82)	-0.15	(-0.15 - 9.75)
Skin melanoma	0	0.60	0.00	(0.00 - 6.50)	-1.52	(-1.52 - 8.38)
Soft tissues	0	0.22	0.00	(0.00 - 17.76)	-0.56	(-0.56 - 9.34)
Prostate	22	12.01	1.83	(1.15 - 2.78) *	25.22	(4.43 - 53.90) *
Testicle	0	0.03	0.00	(0.00 - 134.61)	-0.07	(-0.07 - 9.82)
Kidney	3	1.05	2.85	(0.54 - 8.44)	4.92	(-1.23 - 19.77)
Urinary bladder	12	6.02	1.99	(1.02 - 3.49) *	15.09	(0.37 - 37.88) *
Pelvis, ureter and pathways	1	0.27	3.77	(0.00 - 21.62)	1.86	(-0.67 - 13.80)
Urinary tract	13	6.29	2.07	(1.10 - 3.55) *	16.95	(1.53 - 40.41) *
Encephalon and CNS	1	0.50	2.00	(0.00 - 11.45)	1.26	(-1.26 - 13.21)
Thyroid	2	0.06	33.69	(3.18 - 123.89) *	4.90	(0.33 - 18.42) *
Hodgkin Lymphoma	0	0.07	0.00	(0.00 - 57.12)	-0.17	(-0.17 - 9.73)
Non-Hodgkin Lymphoma	8	1.04	7.70	(3.29 - 15.25) *	17.58	(6.00 - 37.37) *
Multiple myeloma	1	0.62	1.62	(0.00 - 9.31)	0.97	(-1.55 - 12.92)
Leukaemia	1	1.43	0.70	(0.00 - 4.02)	-1.08	(-3.60 - 10.87)
Another	5	4.27	1.17	(0.37 - 2.75)	1.84	(-6.80 - 18.92)
All (excluding no melanoma skin tumours)	**161**	**50.71**	**3.18**	**(2.70 - 3.71) ***	**278.48**	**(218.11 - 346.42) ***

RISK OF A SMN AT WOMEN DIAGNOSED WITH PREVIOUS LARYNX CANCER

SECOND TUMORAL TYPE	OBS	ESP	SIR	SIR (CI 95%)	EAR	EAR (CI 95%)
Lip	0	0.00	0.00	(0.00 - 826.78)	-0.26	(-0.26 - 212.20)
Oral cavity	0	0.01	0.00	(0.00 - 407.36)	-0.52	(-0.52 - 211.93)
Salivary glands	0	0.00	0.00	(0.00 - 999.99)	-0.20	(-0.20 - 212.26)
Oropharynx	0	0.00	0.00	(0.00 - 999.99)	-0.10	(-0.10 - 212.36)
Nasopharynx	0	0.00	0.00	(0.00 - 999.99)	-0.03	(-0.03 - 212.43)
Hypopharynx	0	0.00	0.00	(0.00 - 999.99)	-0.01	(-0.01 - 212.44)
Nasal cavities and sinus	0	0.00	0.00	(0.00 - 999.99)	-0.12	(-0.12 - 212.33)
Larynx	0	0.00	0.00	(0.00 - 999.99)	-0.04	(-0.04 - 212.42)
Head and neck	**0**	**0.02**	**0.00**	**(0.00 - 167.54)**	**-1.27**	**(-1.27 - 211.19)**
Oesophagus	0	0.01	0.00	(0.00 - 695.69)	-0.31	(-0.31 - 212.15)
Stomach	0	0.07	0.00	(0.00 - 54.13)	-3.93	(-3.93 - 208.53)
Colon	0	0.18	0.00	(0.00 - 22.37)	-9.50	(-9.50 - 202.96)
Rectum	1	0.06	16.25	(0.01 - 93.15)	50.86	(-3.31 - 307.31)
Colon, rectum and anus	1	0.24	4.22	(0.00 - 24.20)	41.36	(-12.81 - 297.81)
Liver	0	0.03	0.00	(0.00 - 134.54)	-1.58	(-1.58 - 210.88)
Gallbladder and pathways	0	0.03	0.00	(0.00 - 125.21)	-1.70	(-1.70 - 210.76)
Pancreas	0	0.05	0.00	(0.00 - 78.96)	-2.69	(-2.69 - 209.76)
Lung	0	0.04	0.00	(0.00 - 94.33)	-2.25	(-2.25 - 210.20)
Bone and cartilage	0	0.00	0.00	(0.00 - 999.99)	-0.08	(-0.08 - 212.38)
Skin melanoma	0	0.02	0.00	(0.00 - 166.52)	-1.28	(-1.28 - 211.18)
Soft tissues	0	0.01	0.00	(0.00 - 490.49)	-0.43	(-0.43 - 212.02)
Mammary gland	1	0.26	3.81	(0.00 - 21.83)	39.96	(-14.21 - 296.41)
Cervix	0	0.01	0.00	(0.00 - 261.66)	-0.81	(-0.81 - 211.64)
Uterine body	0	0.07	0.00	(0.00 - 58.79)	-3.61	(-3.61 - 208.84)
Ovary	0	0.04	0.00	(0.00 - 108.29)	-1.96	(-1.96 - 210.49)
Kidney	0	0.02	0.00	(0.00 - 163.60)	-1.30	(-1.30 - 211.16)
Urinary bladder	0	0.05	0.00	(0.00 - 71.95)	-2.95	(-2.95 - 209.50)
Pelvis, ureter and pathways	0	0.01	0.00	(0.00 - 648.88)	-0.33	(-0.33 - 212.13)
Urinary tract	0	0.06	0.00	(0.00 - 64.77)	-3.28	(-3.28 - 209.18)
Encephalon and CNS	0	0.02	0.00	(0.00 - 235.64)	-0.90	(-0.90 - 211.55)
Thyroid	0	0.01	0.00	(0.00 - 507.22)	-0.42	(-0.42 - 212.04)
Hodgkin Lymphoma	0	0.00	0.00	(0.00 - 999.99)	-0.15	(-0.15 - 212.30)
Non-Hodgkin Lymphoma	0	0.03	0.00	(0.00 - 124.19)	-1.71	(-1.71 - 210.74)
Multiple myeloma	0	0.03	0.00	(0.00 - 156.14)	-1.36	(-1.36 - 211.09)
Leukaemia	0	0.04	0.00	(0.00 - 92.67)	-2.29	(-2.29 - 210.16)
Another	0	0.17	0.00	(0.00 - 23.44)	-9.06	(-9.06 - 203.39)
All (excluding no melanoma skin tumours)	**2**	**1.28**	**1.56**	**(0.15 - 5.74)**	**38.95**	**(-59.21 - 329.16)**

RISK OF A SMN AT MEN DIAGNOSED WITH PREVIOUS HEAD AND NECK CANCER

SECOND TUMORAL TYPE	OBS	ESP	SIR	SIR (CI 95%)	EAR	EAR (CI 95%)
Lip	4	1.26	3.17	(0.83 - 8.20)	2.84	(-0.23 - 9.42)
Oral cavity	9	0.76	11.80	(5.35 - 22.49) *	8.55	(3.44 - 17.01) *
Salivary glands	1	0.22	4.50	(0.00 - 25.79)	0.81	(-0.23 - 5.72)
Oropharynx	9	0.48	18.92	(8.58 - 36.07) *	8.84	(3.74 - 17.31) *
Nasopharynx	0	0.07	0.00	(0.00 - 54.90)	-0.07	(-0.07 - 3.99)
Hypopharynx	7	0.34	20.46	(8.11 - 42.39) *	6.91	(2.52 - 14.69) *
Nasal cavities and sinus	0	0.14	0.00	(0.00 - 27.45)	-0.15	(-0.15 - 3.92)
Larynx	12	1.70	7.08	(3.64 - 12.40) *	10.69	(4.64 - 20.06) *
Head and neck	**42**	**4.97**	**8.44**	**(6.08 - 11.42) ***	**38.42**	**(26.23 - 53.79) ***
Oesophagus	24	1.25	19.13	(12.24 - 28.50) *	23.60	(14.63 - 35.80) *
Stomach	6	5.31	1.13	(0.41 - 2.48)	0.72	(-3.27 - 8.13)
Colon	29	13.08	2.22	(1.48 - 3.19) *	16.52	(6.57 - 29.69) *
Rectum	12	5.39	2.23	(1.15 - 3.90) *	6.86	(0.81 - 16.23) *
Colon, rectum and anus	41	18.46	2.22	(1.59 - 3.01) *	23.38	(11.36 - 38.60) *
Liver	6	3.04	1.98	(0.71 - 4.33)	3.07	(-0.91 - 10.49)
Gallbladder and pathways	1	1.29	0.77	(0.00 - 4.43)	-0.30	(-1.34 - 4.61)
Pancreas	5	2.71	1.85	(0.58 - 4.35)	2.38	(-1.17 - 9.40)
Lung	149	16.24	9.18	(7.76 - 10.78) *	137.75	(113.93 - 164.69) *
Bone and cartilage	0	0.13	0.00	(0.00 - 29.89)	-0.14	(-0.14 - 3.93)
Skin melanoma	2	1.40	1.43	(0.13 - 5.26)	0.62	(-1.26 - 6.18)
Soft tissues	0	0.52	0.00	(0.00 - 7.56)	-0.54	(-0.54 - 3.53)
Prostate	46	28.43	1.62	(1.18 - 2.16) *	18.23	(5.43 - 34.20) *
Testicle	0	0.08	0.00	(0.00 - 50.40)	-0.08	(-0.08 - 3.99)
Kidney	6	2.47	2.43	(0.88 - 5.33)	3.67	(-0.32 - 11.08)
Urinary bladder	27	14.14	1.91	(1.26 - 2.78) *	13.35	(3.78 - 26.14) *
Pelvis, ureter and pathways	2	0.63	3.17	(0.30 - 11.66)	1.42	(-0.46 - 6.98)
Urinary tract	29	14.77	1.96	(1.31 - 2.82) *	14.77	(4.81 - 27.94) *
Encephalon and CNS	3	1.19	2.53	(0.48 - 7.48)	1.88	(-0.65 - 7.98)
Thyroid	3	0.15	20.00	(3.77 - 59.19) *	2.96	(0.43 - 9.06) *
Hodgkin Lymphoma	0	0.17	0.00	(0.00 - 22.74)	-0.18	(-0.18 - 3.89)
Non-Hodgkin Lymphoma	12	2.47	4.85	(2.50 - 8.50) *	9.88	(3.84 - 19.25) *
Multiple myeloma	1	1.46	0.69	(0.00 - 3.93)	-0.47	(-1.51 - 4.44)
Leukaemia	1	3.35	0.30	(0.00 - 1.71)	-2.44	(-3.47 - 2.47)
Another	13	9.89	1.31	(0.70 - 2.26)	3.23	(-3.11 - 12.87)
All (excluding no melanoma skin tumours)	**390**	**120.01**	**3.25**	**(2.94 - 3.59) ***	**280.13**	**(240.97 - 322.38) ***

RISK OF A SMN AT WOMEN DIAGNOSED WITH PREVIOUS HEAD AND NECK CANCER

SECOND TUMORAL TYPE	OBS	ESP	SIR	SIR (CI 95%)	EAR	EAR (CI 95%)
Lip	0	0.03	0.00	(0.00 - 122.25)	-0.17	(-0.17 - 20.33)
Oral cavity	1	0.07	14.99	(0.01 - 85.93)	4.88	(-0.35 - 29.62)
Salivary glands	0	0.02	0.00	(0.00 - 173.99)	-0.12	(-0.12 - 20.38)
Oropharynx	0	0.01	0.00	(0.00 - 331.79)	-0.06	(-0.06 - 20.43)
Nasopharynx	0	0.00	0.00	(0.00 - 999.99)	-0.02	(-0.02 - 20.48)
Hypopharynx	0	0.00	0.00	(0.00 - 999.99)	-0.01	(-0.01 - 20.49)
Nasal cavities and sinus	0	0.01	0.00	(0.00 - 300.42)	-0.07	(-0.07 - 20.43)
Larynx	1	0.01	171.76	(0.07 - 984.56)	5.20	(-0.03 - 29.93)
Head and neck	**2**	**0.16**	**12.77**	**(1.20 - 46.95) ***	**9.64**	**(0.17 - 37.63) ***
Oesophagus	4	0.04	110.26	(28.68 - 285.11) *	20.72	(5.25 - 53.88) *
Stomach	0	0.49	0.00	(0.00 - 8.06)	-2.54	(-2.54 - 17.95)
Colon	2	1.15	1.74	(0.16 - 6.41)	4.46	(-5.01 - 32.45)
Rectum	3	0.42	7.13	(1.35 - 21.12) *	13.48	(0.76 - 44.22) *
Colon, rectum and anus	5	1.57	3.19	(1.01 - 7.50) *	17.94	(0.05 - 53.28) *
Liver	0	0.19	0.00	(0.00 - 20.56)	-1.00	(-1.00 - 19.50)
Gallbladder and pathways	0	0.20	0.00	(0.00 - 19.29)	-1.06	(-1.06 - 19.43)
Pancreas	0	0.32	0.00	(0.00 - 12.22)	-1.68	(-1.68 - 18.82)
Lung	1	0.28	3.60	(0.00 - 20.62)	3.77	(-1.45 - 28.51)
Bone and cartilage	0	0.01	0.00	(0.00 - 326.61)	-0.06	(-0.06 - 20.43)
Skin melanoma	1	0.16	6.19	(0.00 - 35.49)	4.38	(-0.84 - 29.12)
Soft tissues	0	0.05	0.00	(0.00 - 78.78)	-0.26	(-0.26 - 20.23)
Mammary gland	9	1.75	5.13	(2.33 - 9.78) *	37.88	(12.16 - 80.53) *
Cervix	1	0.10	9.65	(0.00 - 55.32)	4.69	(-0.54 - 29.42)
Uterine body	1	0.44	2.29	(0.00 - 13.12)	2.94	(-2.28 - 27.68)
Ovary	0	0.25	0.00	(0.00 - 15.64)	-1.31	(-1.31 - 19.18)
Kidney	1	0.15	6.74	(0.00 - 38.63)	4.45	(-0.77 - 29.19)
Urinary bladder	0	0.35	0.00	(0.00 - 11.19)	-1.83	(-1.83 - 18.66)
Pelvis, ureter and pathways	0	0.04	0.00	(0.00 - 89.38)	-0.23	(-0.23 - 20.26)
Urinary tract	0	0.39	0.00	(0.00 - 9.94)	-2.06	(-2.06 - 18.43)
Encephalon and CNS	0	0.12	0.00	(0.00 - 33.40)	-0.61	(-0.61 - 19.88)
Thyroid	2	0.06	33.60	(3.17 - 123.58) *	10.14	(0.67 - 38.14) *
Hodgkin Lymphoma	0	0.02	0.00	(0.00 - 183.34)	-0.11	(-0.11 - 20.38)
Non-Hodgkin Lymphoma	0	0.23	0.00	(0.00 - 16.96)	-1.21	(-1.21 - 19.29)
Multiple myeloma	1	0.17	6.04	(0.00 - 34.63)	4.36	(-0.86 - 29.10)
Leukaemia	0	0.28	0.00	(0.00 - 13.95)	-1.47	(-1.47 - 19.02)
Another	2	1.11	1.81	(0.17 - 6.65)	4.68	(-4.79 - 32.67)
All (excluding no melanoma skin tumours)	**30**	**8.53**	**3.52**	**(2.37 - 5.02) ***	**112.22**	**(61.12 - 179.51) ***

REFERENCES

1. SEOM: Sociedad Española de Oncología Médica [Internet]. [cited 2018 Sept 25]. Available from: http://www.seom.org/en/inicio

2. McGraw-Hill Concise Dictionary of Modern Medicine. S.v. "cancer." Retrieved September 21 2018 from https://medical-dictionary.thefreedictionary.com/cancer

3. McGraw-Hill Concise Dictionary of Modern Medicine. S.v. "second cancer." Retrieved September 21 2018 from https://medical-dictionary.thefreedictionary.com/second+cancer

4. Netter FH. Atlas de Anatomía Humana. 4th ed. Barcelona: Elsevier Masson; 2007.

5. Dakubo GD, Jakupciak JP, Birch-Machin MA, Parr RL. Clinical implications and utility of field cancerization. Cancer Cell Int. 2007; 7:1–12

6. Partridge M, Costea DE, The XH. The changing face of p53 in head and neck cancer. 2007;1123–38.

7. Gregson EM, Bornschein J, Fitzgerald RC. Genetic progression of Barrett's oesophagus to oesophageal adenocarcinoma. Br J Cancer [Internet]. 2016;115(4):403–10. Available from: http://dx.doi.org/10.1038/bjc.2016.219

8. Cuevas Gonzalez JC, Gaitan Cepeda LA, Borges Yanez SA, et al (2016). p53 and p16 in oral epithelial dysplasia and oral squamous cell carcinoma: A study of 208 cases. *Indian J Pathol Microbiol*, 59, 153-8.

9. Zaid KW, Chantiri M, Bassit G (2016). Recombinant human bone morphogenetic protein-2 in development and progression of oral squamous cell carcinoma. *Asian Pac J Cancer Prev*, 17, 927-32.

10. Wood, M. E., Vogel, V., Ng, A., Foxhall, L., Goodwin, P., & Travis, L. B. (2012). Second malignant neoplasms: Assessment and strategies for risk reduction. *Journal of Clinical Oncology*, *30*(30), 3734–3745. http://doi.org/10.1200/JCO.2012.41.8681

11. Global Cancer Observatory from the International Agency for Cancer Research http://gco.iarc.fr/

12. European Cancer Information System https://ecis.jrc.ec.europa.eu/

13. IARC Press. Weight Control and Physical Activity. IARC Handbooks Cancer Prev. 2002;6(International Agency for Research on Cancer, IARC).

14. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults. N Engl J Med. 2003

15. Curtis RE, Freedman DM, Ron E, Ries LAG, Hacker DG, Edwards BK, et al. New malignancies among cancer survivors: SEER cancer registries, 1973-2000. J Epidemiol Community Heal. 2008;62(4)

16. Shiels MS, Gibson T, Sampson J, Albanes D, Andreotti G, Freeman LB, et al. Cigarette smoking prior to first cancer and risk of second smoking-associated cancers among survivors of bladder, kidney, head and neck, and stage I lung cancers. J Clin Oncol. 2014;32(35):3989–95.

17. Marshall JR (ed): Alcohol (ed 3). New York, NY, Oxford University Press, 2006

18. Schottenfeld D. Alcohol as a co-factor in the etiology of cancer. Cancer 43:1962-1966. 1979;

19. León X, Quer M, Diez S, Orús C, López-Pousa A, Burgués J. Second neoplasm in patients with head and neck cancer. Head Neck. 1999;

20. Surgery N, Orleans N, Orleans N. SECOND PRIMARY MALIGNANCIES IN THE HEAD AND NECK CANCER PATIENT. 2015;946–54.

21. Morris LGT, Sikora AG, Patel SG, Hayes RB, Ganly I. Second primary cancers after an index head and neck cancer: Subsite-specific trends in the era of human papillomavirus - Associated oropharyngeal cancer. J Clin Oncol. 2011;29(6):739–46.

22. Maxwell JH, Kumar B, Feng FY, Worden FP, Lee JS, Eisbruch A, et al. Tobacco use in human papillomavirus-positive advanced oropharynx cancer patients related to increased risk of distant metastases and tumor recurrence. Clin Cancer Res. 2010

23. Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst. 2008

24. Travis LB, Rabkin CS, Brown LM, Allan JM, Alter BP, Ambrosone CB, et al. Cancer survivorship - Genetic susceptibility and second primary cancers: Research strategies and recommendations. J Natl Cancer Inst. 2006;98(1):15–25.

25. Altekruse SF, Kosary CL, Krapcho M, et al (eds): SEER Cancer Statistics Review, 1975-2007. National Cancer Institute, Bethesda, MD, 2010. http://seer.cancer.gov/csr/1975_2007/

26. DeVita VT, Hellman S, Rosenberg SA. Cancer: Principles and Practice of Oncology Collections: Clinical Medicine. 2005. 2047-2065.

27. Bernstein JL, Haile RW, Stovall M, Boice JD, Shore RE, Langholz B, et al. Radiation exposure, the ATM gene, and contralateral breast cancer in the women's environmental cancer and radiation epidemiology study. J Natl Cancer Inst. 2010;102(7):475–83.

28. Kovalchik SA, Ronckers CM, Veiga LHS, Sigurdson AJ, Inskip PD, De Vathaire F, et al. Absolute risk prediction of second primary thyroid cancer among 5-year survivors of childhood cancer. J Clin Oncol. 2013;31(1):119–27.

29. National Council on Radiation Protection and Measurements (NCRP): Second Cancers and Cardiovascular Disease After Radiation Therapy. NCRP Report No. 170. Bethesda, MD, NCRP, 2011

30. Leone, G., Pagano, L., Ben-Yehuda, D., & Voso, M. T. (2007). Therapy-related leukemia and myelodysplasia: Susceptibility and incidence. *Haematologica*, *92*(10), 1389–1398. https://doi.org/10.3324/haematol.11034

31. Travis, L. B. (2006). The epidemiology of second primary cancers. *Cancer Epidemiology Biomarkers and Prevention*, *15*(11), 2020–2026. https://doi.org/10.1158/1055-9965.EPI-06-0414

32. Travis LB, Holowaty EJ, Bergfeldt K, et al: Risk of leukemia after platinum-based chemotherapy for ovarian cancer. N Engl J Med 340:351-357, 1999

33. Travis LB, Andersson M, Gospodarowicz M, et al: Treatment-associated leukemia following testicular cancer. J Natl Cancer Inst 92:1165-1171, 2000

34. Watters JW, Kraja A, Meucci MA, Province MA, McLeod HL. Genome-wide discovery of loci influencing chemotherapy cytotoxicity. Proc Natl Acad Sci U S A [Internet]. 2004;101(32):11809–14. Available from: http://dx.doi.org/10.1073/pnas.0404580101

35. AIRTUM Working Group. Italian cancer figures, report 2013: Multiple tumours. Epidemiol Prev [Internet]. 2013;37(4–5 Suppl 1):1–152. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24259384

36. Jégu J, Colonna M, Daubisse-Marliac L, Trétarre B, Ganry O, Guizard AV, Bara S, Troussard X, Bouvier V, Woronoff AS, Velten M. The effect of patient characteristics on second primary cancer risk in France. BMC Cancer 2014, 14:94-107.