**Effect of previous history of cancer on survival of patients with a second cancer of the head and neck**

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**CONFLICT OF INTEREST STATEMENT**

None declared.

**ABSTRACT**

**Objective** - To provide head and neck squamous cell carcinoma (HNSCC) survival estimates with respect to patient previous history of cancer.

**Materials and Methods** -Data from ten French population-based cancer registries were used to establish a cohort of all male patients presenting with a HNSCC diagnosed between 1989 and 2004**.** Vital status was updated until December 31, 2007. The 5-year overall and net survival estimates were assessed using the Kaplan-Meier and Pohar-Perme estimators, respectively. Multivariate Cox regression models were used to assess the effect of cancer history adjusted for age and year of HNSCC diagnosis.

**Results** - Among the cases of HNSCC, 5553 were localized in the oral cavity, 3646 in the oropharynx, 3793 in the hypopharynx and 4550 in the larynx. From 11.0% to 16.8% of patients presented with a previous history of cancer according to HNSCC. Overall and net survival were closely tied to the presence, or not, of a previous cancer. For example, for carcinoma of the oral cavity, the five-year overall survival was 14.0%, 5.9% and 36.7% in case of previous lung cancer, oesophagus cancer or no cancer history, respectively. Multivariate analyses showed that previous history of cancer was a prognosis factor independent of age and year of diagnosis (p <.001).

**Conclusion** -Previous history of cancer is strongly associated with survival among HNSCC patients. Survival estimates based on patients’ previous history of cancer will enable clinicians to assess more precisely the prognosis of their patients with respect to this major comorbid condition.

**Keywords:** Head and neck cancer; survival; neoplasms, second primary; registries.

**INTRODUCTION**

With improvements in cancer survival due to earlier detection and advances in cancer treatments, cancer survivors face an increasing risk of developing second primary cancer (SPC) [1]. In particular, patients with a first cancer related to tobacco and alcohol exposure (such as lung, oesophagus, head and neck cancers) are at greater risk of developing a SPC of the head and neck compared with the general population [2,3]. Most of these SPCs are head and neck squamous cell carcinomas (HNSCC), a type of cancer treated mainly by radiotherapy, surgery and, more recently - for locally advanced disease - chemo radiotherapy or induction chemotherapy followed by radiotherapy based on patient prognosis [4].

However, currently available HNSCC survival estimates may be inappropriate for patients with a HNSCC occurring as a SPC. Indeed, in survival studies based on cancer registry data it is often the practice to restrict the analysis to first primary tumors and to exclude all subsequent primary cancers [5,6]. A more recent approach consists in the inclusion of all primary cancers, irrespective of whether other cancers of a different type have been diagnosed previously in a patient (i.e. patients who had more than one type of cancer are included in different counts) [7,8]. However, these approaches do not consider the history of cancer on survival as, either second HNSCC are excluded, or the estimates of the survivals of patients with a HNSCC occurring as a first or second primary are mixed.

Even if some studies assessed the impact of SPC occurrence on the survival of patients with a first HNSCC [9–12], the survival of patients with a HNSCC diagnosed as a second cancer remains poorly documented. This is a matter of concern as previous history of cancer constitutes one of the major comorbid conditions that can impact HNSCC patients’ prognosis and therapeutic management [13].

Using population-based data from France, where the risk of second HNSCC is particularly high [3], the objective of this study was to provide HNSCC survival estimates with respect to patient previous history of cancer. Moreover, the effect of covariates on survival was assessed, including the length of time between the first cancer and the HNSCC diagnosis.

**MATERIAL AND METHODS**

Data from ten French population-based cancer registries belonging to the Francim cancer registries network were used to establish a cohort of all male patients diagnosed with HNSCC between 1989 and 2004. These registries cover eight administrative regions of France (Bas-Rhin, Calvados, Doubs, Hérault, Isère, Manche, Somme and Tarn), which comprise six million inhabitants, or 9.6% of the mainland French population. Quality of data was checked both at the registry level and for the whole common database of Francim. These registries have a high degree of case ascertainment completeness and incidence data are regularly included in the *‘Cancer Incidence in Five Continents’* monograph series [14]. Moreover, data from these registries were recently used to assess second primary cancer incidence [3] and cancer survival in France [15,16].

Invasive squamous cell carcinomas *(International Classification of Diseases for Oncology*, 3rd edition (ICD-O-3) histology codes 80703–80763, 80783) [17] localized at the oral cavity, oropharynx, hypopharynx and larynx (ICD-O-3 site codes C01–C06, C09–C10, C12–C13 and C32, respectively) were included. Oesophagus, colorectum, lung, prostate and bladder cancers were defined in accordance with topography and morphology codes used in the EUROCARE project [5]. Included patients could present with a previous history of HNSCC, but not of the same subsite (i.e. oral cavity, oropharynx, hypopharynx and larynx), in compliance with the International Agency for Research on Cancer registration rules, which recommends to not record second primary cancers occurring in the same site than a first cancer if the histology is similar [18]*.* All available data on invasive cancer cases diagnosed before 1989 were used to define previous history of cancer. The cancer registries were established between 1975 and 1983 (i.e. at least five years before 1989), with the exception of the Manche cancer registry, set up in 1994.

The study concentrated on male patients, as the incidence of HNSCC is scarce among females (incidence rates were of 5 per 100,000 inhabitants in 1995 among females compared with 45 per 100,000 among males [19]), which did not allow reliable estimates of survival with respect to previous history of cancer. Finally, tumor stage, tobacco or alcohol consumption and cancer treatments were not analyzed because detailed data about these exposures were not available. Third- and higher ranked tumors, although not excluded, were not particularly analyzed.

An active follow-up for vital status at December 31, 2007 was carried out for all HNSCC diagnosed between January 1, 1989 and December 31, 2004 using a single standardized procedure, as previously reported [15,16]. Survival time began at date of HNSCC diagnosis (diagnosed as a first or second cancer) and ended at the date of death, last known vital status or December 31, 2007, whichever came first. The proportion of patients with an HNSCC lost to follow-up (i.e. alive at some date before December 31, 2007) was 1.1%.

Firstly, 5-year overall survival was assessed using the Kaplan-Meier estimator. Estimates were stratified by whether patient had previous cancer, previous cancer site and age group (≤54 years, 55-64 years, ≥65 years). Secondly, net survival was computed using the Pohar-Perme estimator of the net cumulative rate [20]. This estimate corresponds to hypothetical survival in which patients could only die from their cancer; i.e. rates of death from other causes, as given in the general population life tables, are removed. Under its assumptions, net survival can be considered as an estimate of cancer-specific survival. The life tables were available by gender, age, calendar year and French administrative region. Finally, multivariate Cox regression models were used to assess the cancer history effect while adjusting for age and year of HNSCC diagnosis. Adjustment on the other comorbidities (e.g. chronic pulmonary or cardiovascular diseases) could not be performed because such detailed data were not available in this population-based study. Hazard ratios (HR) and their respective 95% confidence intervals (95% CI) were provided by these models. The effect of time of first primary to HNSCC diagnosis on survival was assessed in patients with a previous history of cancer. All analyses were performed using Stata (version 12.1, Stata Corp, College Station, Texas, USA), with the stns package for net survival estimates [21].

**RESULTS**

Among the cases of HNSCC included, 5553 were localized in the oral cavity, 3646 in the oropharynx, 3793 in the hypopharynx and 4550 in the larynx. Patients’ characteristics by site are presented in Table 1. Overall mean age at HNSCC diagnosis was 60 years-old. It is remarkable that 11.0% to 16.8% of patients presented with a history of cancer according to tumor site. The median length of time between the two cancers ranged from 20.6 to 36.4 months, depending on HNSCC site. Among these patients, previous HNSCC, lung cancer or oesophagus cancer were more frequently reported.

Overall 5-year survival estimates are presented in Tables 2 to 5 for patients diagnosed between 1989 and 2004 with a cancer of the oral cavity, oropharynx, hypopharynx and larynx, respectively. Generally speaking, patients with an HNSCC of the larynx presented the highest 5-year survival (47.6%), followed by patients with a cancer of the oral cavity (34.0%), oropharynx (29.7%) and hypopharynx (23.5%).

Striking differences in patient’s prognosis were observed, depending on the type of previous cancer. For example, as reported in Table 2, the survival of patients with a cancer of the oral cavity was greatly reduced among patients with a previous history of HNSCC (5-year survival ranging from 17.2% to 27.4%, depending on HNSCC site), lung cancer (14.0%) or oesophagus cancer (5.9%), compared with patients with no previous history of cancer (36.7%).

Interestingly, among patients with a cancer of the hypopharynx (table 4), patients with a previous cancer of the oral cavity or larynx did not seem to present a worse 5-year survival compared with patients with no previous cancer history (23.1% and 25.4% versus 24.5%).

Although most estimates of 5-year survival by age at HNSCC diagnosis are presented in Tables 2 to 5, these estimates could not be provided for some age classes, given the reduced number of cases.

For international comparison purposes, net survival estimates by site of HNSCC are provided in Supplementary Material 1 to 4. Because net survival corresponds to survival in a hypothetical world where patients could only die from their cancer, net survival estimates are slightly higher compared with overall survival estimates previously reported. As expected, greater differences between these two indicators can be seen among older patients. For example, for cancer of the oropharynx, 5-year overall survival was respectively 35.1% and 22.7% (Table 3) among ≤54 years-old and ≥65 years-old patients, compared to 5-year net survival of 36.1% and 28.2% (Supplementary Material 2) among these patients.

The results of multivariate Cox regression models by site of HNSCC are presented in Table 6. Age at diagnosis of HNSCC was, unsurprisingly, associated with survival (likelihood-ratio test p<.001), older patients showing a worse prognosis than younger ones, irrespective of the sub-site of HNSCC. Compared with the 1989-1994 period, the survival of patients diagnosed during the period 2000-2004 period improved for oral cavity (HR=0.90, 95% CI [0.83-0.97]), oropharynx (HR=0.89, 95% CI [0.82-0.99]) and larynx cancers (HR=0.89, 95% CI [0.81-0.98]), but not for hypopharynx cancer (HR=1.02, 95% CI [0.93-1.11]).

Multivariate analyses confirmed the effect of previous history of cancer on survival adjusted for age and year of HNSCC diagnosis. Indeed, patients with previous history of cancer presented a worse survival than patients with no previous cancer (p <.001). Particularly higher risks of death were observed among patients with a previous oesophagus or lung cancer compared with patients with no previous history of cancer (e.g. among patients with an oral cavity cancer, HR of 2.53 and 1.78, respectively). Among patients with a hypopharynx cancer, patients with a previous cancer of the oral cavity or of the larynx had similar survival to those with no previous history of cancer (HR=1.12, 95% CI, 0.95-1.34 and HR=0.92, 95% CI, 0.69-1.22, respectively).

Finally, the effect on survival of the length of time between the first cancer and the HNSCC diagnosis adjusted on age, year of HNSCC diagnosis and first cancer site are presented in Figure 1. Although HR estimates were not particularly conclusive due to the restriction of the sample analyzed to patients with a previous history of cancer (sample size ranging from 489 to 931 depending on HNSCC site), it seems that a greater length of time (≥ 5 years, taken as reference category here) was associated with a better prognosis, especially among patients with an oropharynx cancer (p=.032).

**DISCUSSION**

This study provides, for the first time, 5-year survival estimates for patients diagnosed with a HNSCC with respect to their previous history of cancer. It shows that previous history of cancer is a prognosis factor independent of age and year of diagnosis and that the impact of a former cancer on survival is closely tied to first cancer site.

The 5-year overall and net survival estimates reported here (e.g. 34.0% and 37.0% for oral cavity cancer) are very similar to those published in a recent French study including a larger number of cancers registries (36% and 39% for oral cavity cancer) [22]. Although the effects of a previous cancer on cancer survival for breast, prostate, colorectal and lung cancers have been reported [23–28], there is, to date, no population-based study providing HNSCC survival estimates with which to compare our results in respect of the previous history of cancer.

Considering survival from the diagnosis date of a subsequent HNSCC complements studies that assess the effect of a second primary cancer on the survival of patients first diagnosed with HNSCC [9–12]. Indeed, the estimates provided in our study take into account data about former cancers on survival estimates, which fit very well with the clinical situation where physicians gather data about patients’ medical history in order to establish a prognosis and an optimal treatment strategy.

Studies about comorbidity in head and neck cancer may constitute work closely related to this topic. Indeed, the term “comorbidity” refers to disease processes that coexist and are not related to the index disease being studied [13]. Most of the comorbid illnesses among HNSCC patients (such as chronic pulmonary disease, cardiovascular disease or previous cancer) are related to a history of alcohol and tobacco abuse [29]. The Charlson Index, validated for use in HNSCC, is one of the indices most frequently used [30,31] and many studies have shown that comorbidities influence survival negatively [13]. However, the specific contribution of previous history of cancer to HNSCC survival remains poorly understood, as the effect of previous history of cancer is mixed with other comorbid conditions within comorbidity indices. Moreover, there is little distinction between first cancer site in these indices as, in the weighted Charlson Index, the previous history of cancer accounts for 2 points for “any tumor”, ”leukemia” or “lymphoma” and 6 points for “metastatic solid tumor” [30]. This is a matter of concern for prognostication, given that we found in our study that cancer survival was more or less impacted depending on the location of the first cancer site. Finally, although comorbidity indexes are useful in summing up the information about various diseases according to one prognosis criterion, it appears that prognostication of HNSCC patients may also benefit from the availability of survival indicators detailed by first cancer history.

In our study, the survival of HNSCC patients with a history of cancer may be influenced by three distinct effects, two of which result in lower survival probability.

Firstly, the survival of patients with a HNSCC diagnosed as a second cancer could be influenced by the excess mortality arising from their first cancer. This is particularly the case for a first cancer site with a bad prognosis, such as lung cancer or oesophagus cancer. Indeed, the 5-year net survival ranged from 11.5% to 25.3% for lung cancer and 6.1% to 16.2% for oesophagus cancer, depending on the site of HNSCC in our study. Finally, these survival probabilities are close to the 5-year net survival estimates of 13% for lung and 12% for oesophagus cancers among men in France [22]. In case of former lung cancer or oesophagus cancer, the relative short length of time between the first cancer and the subsequent HNSCC may explain the fact that the prognosis of these patients is close to the prognosis of their first cancer. Indeed, depending on HNSCC site, the median length of time between the two cancers ranged from 0.8 to 4.4 months for oesophagus cancers and from 5.5 to 22.7 months for lung cancer.

Secondly, it is possible that the sequel of a former cancer, such as low performance status, altered nutritional state or presence of comorbidities, may lead to a suboptimal treatment for HNSCCs diagnosed as a subsequent cancer and resulted in a decrease of survival. Indeed, studies suggested that the degree of comorbidity (which includes previous history of cancer) may have an impact on treatment options, with up to 20% of patients receiving suboptimal treatment [13]. HNSCCs are treated mainly by radiotherapy, surgery and, more recently, for locally advanced disease, chemo radiotherapy or induction chemotherapy followed by radiotherapy based on patient prognosis [4]. For instance, it is possible that a surgery or radiotherapy performed for the treatment of a former cancer of the head and neck or the oesophagus may rule out a complete surgical resection of a subsequent HNSCC. In some cases, the renal function of the patient may have been damaged by chemotherapy used to treat a previous cancer, thus limiting the subsequent use of chemotherapy or chemoradiotherapy containing cisplatin.

Thirdly, the surveillance during the follow-up of a first cancer may have led to an early detection of a new HNSCC at a more localized stage, resulting in a better prognosis. The multivariate analyses showed that, for hypopharynx cancers, patients with a previous cancer of the oral cavity or of the larynx had survival similar to the survival of patients with no previous history of cancer. These results are consistent with those reported by Aguiló et al., where lung cancer patients with multiple cancers had a slightly higher survival than patients with lung cancer as a unique primary [28]. Given that tobacco and alcohol consumption is estimated to be responsible for 72% of head and neck cancers in the general population, (with 4% due to alcohol alone, 33% due to tobacco alone, and 35% due to tobacco and alcohol combined, as reported by the International Head and Neck Cancer Epidemiology (INHANCE) consortium [32]), a specific surveillance of cancer survivors with a high consumption of tobacco and alcohol may allow the early detection of subsequent HNSCC and thereby improve patient prognosis.

Our study has several limitations. Firstly, it is possible that more recently established cancer registries may wrongly consider some of the second-ranked HNSCC as HNSCC with no previous history of cancer if the first cancer diagnosed among patients is anterior to the beginning of the registration period. In order to appreciate the direction and the magnitude of this bias, we conducted a sensitivity analysis restricted to the cases registered after 1989 for tumor rank determination. We found that the percentage of patients with no history of cancer was overestimated by 1.8% to 4.1%, depending on the HNSCC site. Consequently, the survival of patients with no history of cancer was slightly underestimated (from 0.1% to 0.7% concerning the 5-year overall survival). The survival estimates by site of former cancer was not particularly affected. Most of the registries were, in fact, well-established before 1989, with the exception of the Manche cancer registry, set up in 1994. Considering that cases from the Manche cancer registry only represent 7.1% to 8.9% of our cohort, depending on HNSCC site, the overall magnitude of this bias should finally be very small.

Secondly, patients with two cancers related to tobacco and/or alcohol shall present strong comorbid conditions related to these heavy exposures, which suggests that the expected mortality rates extracted from life tables in the general population may underestimate the other cause mortality rates experienced by these patients. Consequently, it cannot be excluded that net survival may underestimate cancer-specific survival among these patients. For these patients, cause of death would have been interesting, but unfortunately this information (usually extracted from death certificates) was not available. However, it should be noted that this would not bias overall survival, as the computation of this indicator does not require the use of expected mortality rates.

Finally, prognosis of HNSCC patients is known to be influenced by a wide range of characteristics such as site, stage, aggressiveness of the tumor, age, performance status and comorbidities [29]. With regard to the stage, population-based studies, otherwise known as “high resolution studies”, may be conducted in order to provide specific cancer survival estimates detailed by stage of the tumors [33]. However, the realization of these studies requires the sampling of cancer cases and complementary data collection - and thus specific funding - that may be problematic. The same concern arises when we try to collect the Charlson comorbidity index in a population-based study [34]. Our study, based on follow-up data of general cancer registries for standard survival assessment, has the merit of providing accurate estimates for patients with previous history of cancer without the need to collect additional data.

In conclusion, this work provides first population-based survival estimates for HNSCC patients based on their previous history of cancer. By assessing the effect of previous cancer on HNSCC patients’ survival, these estimates will enable clinicians to assess more precisely the prognosis of their patients based on this major comorbid condition. Complementary data collection at a population-based level should be sustained to extend this kind of analysis to other comorbidities that can impact therapeutic management and prognosis.

**ACKNOWLEDGMENTS**

This work was carried out within the framework of a four-institute research-program partnership that involved the Institut National du Cancer (INCa), the Institut de Veille Sanitaire (InVS), the French Network of Cancer Registries (FRANCIM) and the Hospices Civils de Lyon. We are grateful to all the pathologists, public hospitals, private hospitals, oncologists and general practitioners for their contribution.

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