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Trends over three decades of the risk of second primary cancer among patients with head and neck cancer

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SUMMARY

Objectives: Patients with a head and neck squamous cell carcinoma (HNSCC) carry a high risk of second primary cancer (SPC). In recent years, a rise in incidence of human papillomavirus (HPV)-associated HNSCC has been recorded. Moreover, tobacco and alcohol consumption levels have changed and major advances have been made in radiation treatment approaches. This raises the question of a modification to the risk of SPC, taking into account variations of patient characteristics related to the HPV-cancer epidemic.

Materials and methods: All patients with a first HNSCC diagnosed between 1975 and 2006 in the French Bas-Rhin region were followed up for 10 years. Multivariate Poisson regression models were used to model standardized incidence rates and excess absolute risks (EARs) over years of diagnosis, taking into account confounders such as sex, age, subsite of first HNSCC and follow-up.

Results: Among these 6258 patients, 1326 presented with a SPC. High EAR values were observed for SPC of lung, head and neck, and esophagus sites (EAR of 172.8, 159.3 and 72.5 excess cancers per 10,000 person-years, respectively). Multivariate analysis showed that the excess risk of SPC of head and neck ($P < .001$) and esophagus ($P = .029$) sites decreased, with 53% lower EARs values in 2000–2006 compared to 1975–1979. In contrast, the excess risk of SPC of the lung did not change significantly ($P = .174$).

Conclusions: Efforts made by public health policy-makers and oncology care providers should be sustained to develop effective smoking cessation interventions, as the excess risk of lung SPC remains high and unchanged.

Introduction

It is currently well established that head and neck cancer survivors face a dramatically high lifetime risk of developing a second primary cancer (SPC).[1–4] This is a matter of concern, as an estimated 635,000 new head and neck cancers were diagnosed worldwide in 2008, including 47,500 cases in the USA and 95,500 in Europe.[5–7] In France particularly, incidence of head and neck cancers is among the highest in Europe, after Eastern European countries.[7] More precisely, among males in the French administrative region of Bas-Rhin, age-standardized incidence rates of tongue, mouth, tonsil, oropharynx, hypopharynx and larynx cancers in 1998–2002 were, respectively, 5.0, 6.8, 2.8, 3.5, 8.0 and 6.4 per 100,000 per year, compared to 2.8, 2.2, 1.7, 0.3, 1.0 and 4.7 in the 9-registries area of the Surveillance, Epidemiology, and End Results Program (SEER Program).[8] Almost all these cases are head and neck squamous cell carcinomas (HNSCC), a type of cancer strongly associated with tobacco and alcohol consumption, and treated mainly by radiotherapy, surgery and, more recently for locally advanced disease, concurrent induction chemotherapy or chemoradiotherapy.[9] An extensive literature shows that patients with a first HNSCC are strongly at risk of developing a SPC of the lung, esophagus and head and neck sites, which is related to shared etiologic factors such as tobacco and alcohol exposure[1–3,10] or late adverse effects of radiotherapy.[11]

Over the past decade, a rise in incidence of human papillomavirus (HPV)-associated oropharyngeal squamous cell cancers in white men younger than 50 years of age has been recorded.[12]

Abbreviations: SPC, second primary cancer; HNSCC, head and neck squamous cell carcinoma; SIR, standardized incidence ratio; EAR, excess absolute risk; PYR, person-years at risk; CI, confidence interval; m, months; y, years; ref, reference category.

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Tobacco and alcohol consumption levels have changed in the general population,[13] and major advances in radiation treatment approaches have coincided with the improvement of imaging and radiation delivery, increasing the dose delivered to target tumor tissues while reducing the dose on adjacent non-target tissues.[9] Moreover, publication of studies highlighting the importance of smoking cessation and alcohol abstinence after a HNSCC diagnosis may have strengthened lifestyle change interventions provided by oncology care providers.[10,14,15]

This raises the question of how the risk of SPC has changed over past decades taking into account variations of patient characteristics (sex, age, subsite of index HNSCC) related to HPV-cancer epidemic, which will be the purpose of this paper.

Material and methods

A population-based cohort of all patients with a first HNSCC diagnosed between 1975 and 2006 in the French administrative region of Bas-Rhin was established using the Bas-Rhin population-based cancer registry database. This registry has achieved a high degree of completeness of ascertainment and incidence data are regularly included in the Cancer Incidence in Five Continents monograph series.[8] All patients were followed-up for 10 years or until December 31, 2006. HNSCC included here were squamous-cell carcinomas (International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) histology codes 8070–8076, 8078)[16] localized at the oral cavity, oropharynx, hypopharynx and larynx (ICD-O-3 site codes C01–C06, C09–C10, C12–C13, C32).

Coding of multiple primaries followed the common set of rules proposed by the International Agency for Research on Cancer (IARC). These rules define multiple primaries as two or more tumors arising in different sites, or at the same site when the histology is different.[17] A SPC was defined as the first subsequent primary cancer occurring at least 2 months after first cancer diagnosis, according to the methods used by Curtis et al.[2] Consequently, the person-year at risk (PYR) for each individual began at 2 months of follow-up, and ended at the date of SPC diagnosis, last known vital status, death, the end of the 10 years-period of follow-up, or December 31, 2006, whichever came first.

The standard "person-year approach" to study SPC incidence was used.[2,18] Following this method, the number of observed SPC (O) was compared to the number expected (E) if patients with a first HNSCC had experienced the same cancer rates as the general population without cancer (allocated by sex, attained age and year of follow-up). This enables a calculation of the observed to expected ratio (O/E ratio), also called standardized incidence ratio (SIR), which can be interpreted as the relative risk of SPC among patients with a first HNSCC compared to the general population without cancer. Another relevant indicator provided by this method is the Excess Absolute Risk (EAR), which is the absolute number of excess cancer cases per PYR among cancer patients. The EAR may be of interest for clinical and public health purposes, as this indicator takes into consideration the frequency of the pathology in the reference population, leading to small values of EARs for scarce sites of SPCs.

The first stage was to compare patient characteristics across year of index HNSCC diagnosis by using the χ^2 test.

Univariate estimations of SIR and EAR values were then computed according to main sites of SPC (all SPC sites, lung and bronchus, HNSCC, esophagus), stratified by sex, age, subsite of index HNSCC, year of index HNSCC diagnosis and follow-up.

Finally, multivariate special Poisson regression models described by Breslow and Day, Dickman et al. and adapted by Reulen et al. to the field of SPC incidence were used.[18–21] These models, as opposed to standard Cox regression models, enable an integration of the number of expected cancers in the general population, and thus a modeling of SIR and EAR values directly. SIR and EAR were modeled by main sites of SPC (all SPC sites, lung and bronchus, HNSCC, esophagus) and adjusted for sex, age, subsite of index HNSCC, year of index HNSCC diagnosis and follow-up.

Byar's accurate approximation to the exact Poisson distribution was used to compute 95% confidence intervals (95% CI) of SIRs values.[18] With respect to Poisson regression models, assumptions were made that the risk of SPC was constant within each follow-up interval, and that the risk of SPC for any two patient subgroups was proportional over follow-up time. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

Results

A total of 7329 patients with a first HNSCC were diagnosed in Bas-Rhin between 1975 and 2006. During the first 2 months after HNSCC diagnosis, 948 (12.9%) patients died (among them, 456 presented a synchronous SPC), 38 presented a synchronous SPC without dying (0.5%), and 85 were lost to follow-up (1.2%).

Characteristics of the 6258 followed-up patients by year of index HNSCC diagnosis are presented in Table 1. The great majority of these patients were males (90.8%), and the mean age at diagnosis was 57.6 years (standard deviation 10.6). All the considered patient characteristics changed over the year of index HNSCC diagnosis (all $P < .001$). In recent periods of diagnosis, there were more female (15.7% in 2000–2006 versus 5.4% in 1975–1979) and older patients (20.7% $\geqslant$70 year old patients in 2000–2006 versus 13.8% in 1975–1979). Interestingly, the relative frequency of HPV-specific subsites increased, with 22.9% of index HNSCC located in the oropharynx in 2000–2006, compared to 17.8% in 1975–1979.

In this cohort, 1326 patients presented a SPC during the first 10 years after index HNSCC diagnosis, compared to 284 expected in the general population without cancer, leading to a relative risk (or SIR) of 4.7 (95% CI, 4.4-4.9) as shown in Table 2. The excess risk of SPC was major, with an EAR of 456.2 excess cancers per 10,000 PYR. As expected, high EAR values were observed for SPC of lung and bronchus, head and neck, and esophagus sites (EAR of 172.8, 159.3 and 72.5 excess cancers per 10,000 PYR, respectively).

Results of univariate analyses showed that estimated SIRs and EARs differed over the years of index HNSCC diagnosis (Table 2). However, SIR and EAR values were also associated with patient characteristics like age, sex, HNSCC subsite and follow-up, with lower excess risk among females, older patients, patients with a first larynx cancer, and longer follow-up. As HNSCC patients characteristics changed over time, a multivariate approach was advisable in order to take into account these potential confounders while studying trends in SPC risk.

Results of multivariate Poisson regression models are presented in Table 3. These models assessed simultaneously the effect of sex, age, subsite of HNSCC, year of diagnosis and follow-up on SIR and EAR values. These models provide ratios of SIRs and ratios of EARs. For example, a ratio of EARs of 0.57 for female patients means that the EAR is 43% lower in female patients compared to male patients (reference category), adjusted for age, subsite of HNSCC, year of diagnosis and follow-up.

Considering all SPC sites, one striking result is that all considered factors (sex, age, subsite of index HNSCC, year of diagnosis and follow-up) were simultaneously associated with SIR and EAR values. Moreover, risk of SPC varied according to year of index HNSCC diagnosis, both SIR ($P = .001$) and EAR ($P = .013$) increasing from 1975–1979 to 1985–1989, and then decreasing until 2000–2006.