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Alcohol and cigarette consumption predict mortality in patients with head and neck cancer: a pooled analysis within the International Head and Neck Cancer Epidemiology (INHANCE) Consortium


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Background: This study evaluated whether demographics, pre-diagnosis lifestyle habits and clinical data are associated with the overall survival (OS) and head and neck cancer (HNC)-specific survival in patients with HNC.

Patients and methods: We conducted a pooled analysis, including 4759 HNC patients from five studies within the International Head and Neck Cancer Epidemiology (INHANCE) Consortium. Cox proportional hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were estimated including terms reported significantly associated with the survival in the univariate analysis.

Results: Five-year OS was 51.4% for all HNC sites combined: 50.3% for oral cavity, 41.1% for oropharynx, 35.0% for hypopharynx and 63.9% for larynx. When we considered HNC-specific survival, 5-year survival rates were 57.4% for all HNC combined: 54.6% for oral cavity, 45.4% for oropharynx, 37.1% for hypopharynx and 72.3% for larynx. Older ages at diagnosis and advanced tumour staging were unfavourable predictors of OS and HNC-specific survival. In laryngeal cancer, low educational level was an unfavourable prognostic factor for OS (HR ¼ 2.54, 95% CI 1.01–6.38, for high school or lower versus college graduate), and status and intensity of alcohol drinking were prognostic factors both of the OS (current drinkers HR ¼ 1.73, 95% CI 1.16–2.58) and HNC-specific survival (current drinkers HR ¼ 2.11, 95% CI 1.22–3.66). In oropharyngeal cancer, smoking status was an independent prognostic factors for OS. Smoking intensity (>20 cigarettes/day HR ¼ 1.41, 95% CI 1.03–1.92) was also an independent prognostic factor for OS in patients with cancer of the oral cavity.

Conclusions: OS and HNC-specific survival differ among HNC sites. Pre-diagnosis cigarette smoking is a prognostic factor of the OS for patients with cancer of the oral cavity and oropharynx, whereas pre-diagnosis alcohol drinking is a prognostic factor of OS and HNC-specific survival for patients with cancer of the larynx. Low educational level is an unfavourable prognostic factor for OS in laryngeal cancer patients.

Key words: head and neck cancer, prognostic factors, pooled analysis, epidemiology

Introduction

Squamous cell carcinoma of the head and neck (HNC) is the seventh common cancer worldwide [1], with 600,000 new cases diagnosed each year worldwide. HNC is the eighth leading cause of cancer death [1]. HNC includes different types of cancers, of which the most frequent are cancers of the oral cavity, oropharynx, hypopharynx and larynx.

The overall survival (OS) rate for these neoplasms has improved over the last decades, but still differs depending on the HNC sub-site [2]. For patients with oral cavity, oropharyngeal and hypo-pharyngeal cancer, an improvement in the 5-year survival was observed in most European countries, while for patients with laryngeal cancer the improvement was less evident [3]. In Europe, 5-year survival rates were 45% for oral cavity, 39% for the oro-pharynx, 25% for the hypopharynx.
59% for the larynx [3]. In developing countries, the survival for patients with these tumours is still lower than in developed countries [4].

HNC patients are also likely to have a high chance of recurrence and second primary cancers involving particularly the head and neck, lung, and oesophagus [5]. Survival of patients with HNCs and second primary cancers has been shown to be poorer than survival of HNC patients without second primary cancers. Second primary cancers within the head and neck region were associated with a better prognosis than those outside this anatomic region [6].

Several lifestyle factors such as tobacco smoking and alcohol drinking, which are the main risk factors for HNC [7, 8], together with diet [9, 10] and physical activity [11] were related with the prognosis of these cancers [12, 13]. In addition, a recent study reported that socioeconomic status (SES) was associated with survival in univariate analysis. However, the effect disappeared after accounting for age, gender, TNM stage, smoking and alcohol [14].

To date, very few large studies have examined the role of prognostic factors for HNC on survival from these neoplasms. The aims of this study are to investigate the OS and cancer-specific survival in a large cohort of HNC patients within the International Head and Neck Cancer Epidemiology (INHANCE) Consortium, and to identify independent prognostic factors for HNC subsites.

Materials and methods

We conducted a pooled analysis using data from five studies within the INHANCE Consortium [15]: Milan (Italy), Rome (Italy), Western Europe involving three Italian centres [Aviano (Friuli Venezia Giulia), Padua (Veneto), Turin (Piemonte)], Sao Paulo (Brazil) and Japan. The studies were approved by the local ethics committees. The recruitment was conducted from 2002 to 2005 in Aviano and Padua, from 2003 to 2005 in Turin, from 2001 to 2009 in Milan, from 2002 to 2014 in Rome, from 2012 to 2011 and from 2011 to 2014 in Sao Paulo and from 2001 to 2005 in Japan.

In each study, patients with histologically confirmed primary squamous cell carcinoma of HNC were included.

The tumours were staged according to the tumour, node, metastasis (TNM) classification [16] and classified into anatomic site according to the following ICD-O-2 codes: oral cavity (C00.3–C00.9, C02.0–C02.3, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C06.0–C06.2, C06.8 and C06.9), oropharynx (C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0–C10.4, C10.8 and C10.9), hypopharynx (C12.9, C13.0–C13.2, C13.8 and C13.9), oral cavity or pharynx overlapping or not otherwise specified (C02.8, C02.9, C05.8, C05.9, C14.0, C14.2 and C14.8) and larynx (codes C32.0–C32.3 and C32.8–C32.9).

Data collection

Information on demographics, lifetime alcohol and tobacco consumption, and other selected lifestyle habits were collected by trained interviewers or medical doctors. Health behaviours focused on the time period ending 1 year before diagnosis. These data were previously pooled and managed by the INHANCE consortium coordination.

Participants were followed from the date of diagnosis to the date of death or to the end of follow-up, whichever occurred first. Death certificate data were also used for mortality, and the cause of death was coded according to the International Classification of Diseases, Ninth Revision. Data on tumour pathology were obtained from pathology records.

All the follow-up information collected was shared by each study with the coordinating centre at the Università Cattolica del Sacro Cuore in Rome, Italy. All data were checked for internal consistency, and clarifications were requested from the original investigators when needed.

Outcome and variables definition

The primary endpoint was the OS, defined as the time from the date of initial diagnosis of HNC primary tumour to the date of death from any cause or last follow-up. The secondary endpoint was the HNC-specific survival, defined as the time from the date of initial diagnosis of HNC primary tumour to the date of death from HNC or last follow-up. With respect to smoking, patients were classified as never, former or current smokers. Frequency of tobacco consumption (never smokers, _20 cigarette-ettes/day, >20 cigarette-ettes/day) and smoking duration in years (never smokers, _20, >20) were also calculated. With respect to alcohol drinking, subjects were classified as never, former or current drinkers, and according to alcohol consumption (none, _1 drink equivalent/day, >1 drink equivalent/day).

Statistical analysis

We used the Kaplan-Meier method to calculate the cumulative proportion surviving and to plot the survival curves. We compared the survival curves using log-rank test and Wilcoxon Breslow Gehan test where appropriate. We used the Cox proportional hazards model to determine independent predictors of OS and HNC-specific survival. We tested the Cox proportional hazards assumption for each covariate using Schoenfeld residuals [17]. We adjusted hazard ratios (HRs) for the OS and HNC-specific survival for the variables that were significantly associated with the OS and HNC-specific survival in the univariate analysis. Furthermore, in order to account for different treatment access and types, the multivariable models were adjusted also by study centre. In the HNC-specific survival analysis, we excluded the Japanese study because the information on cause of death was not available. In the multivariable analysis, for both the OS and HNC-specific survival, we excluded the Milan study because information on tumour stage was not available. We carried out analyses for all studies together, considering overall HNC and individual subsites (oral cavity, oropharynx, hypopharynx, larynx). We conducted all statistical analyses using Stata software (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).
Results
A total of 4759 HNC cases were pooled from seven participating centres. For 540 (15.7%) patients from the Brazilian centre and 21 (2.0%) patients from the Italian centre the date of diagnosis or the date of death was not available and were therefore excluded, resulting in 4198 (88.2%) eligible patients in the analysis (Table 1). Most of the patients were from the Sao Paulo study (68.9%), 24.1% from Italy (Milan, Rome, Aviano, Turin, Padua) and the remainder-17.0% from Japan. Disease location was oral cavity in 1404 (35.6%) patients, oropharynx in 834 (21.1%) patients, hypopharynx in 260 (6.6%) patients, larynx in 1332 (32.8%) patients and oral cavity or pharynx not otherwise specified in 252 (6.0%) patients.

Median age was 59 years (63 for Italy, 61 for Japan and 57 for Brazil) with a higher prevalence of males (77.8%). The Italian studies and the Japanese study were entirely composed of patients with white and Asian ethnicity, respectively; the Brazilian study had a higher prevalence of white ethnicity (68.8%), followed by mulatto (18%), black (8.6%) and others (4.6) (data not shown).

Table 2 reported the median follow-up time and the number of deaths by tumour site and study. A total of 1924 patients (45.8%) died during the follow-up, of whom 1408 died from HNC. Percentages of deaths from all causes in the HNC subsites were 45.2% for oral cavity, 53.5% for oropharynx, 60.1% for hypo-pharynx and 36.2% for larynx.

Five-year OS for all HNC sites combined was 51.4% (50.3% for oral cavity, 41.1% for oropharynx, 35.0% for hypopharynx and 63.9% for larynx; Figure 1). When we considered the HNC-specific survival, 5-year survival rate was 57.4% for all HNC combined (54.6% for oral cavity, 45.4% for oropharynx, 37.1% for hypopharynx and 72.3% for larynx; Figure 2). The survival differs according to study centre: patients from the Japanese centre reported the highest survival (P < 0.0001) while patients from the Brazilian centre reported the lowest survival (P < 0.0001).

The distributions of selected covariates and adjusted HRs for all-cause mortality by tumour site and considering HNC overall are presented in Table 3. Multivariate analysis suggested that increasing age at diagnosis was associated with a reduced OS for HNC overall (HR ¼ 1.02, 95% CI 1.01–1.03), for oral cavity cancer (HR ¼ 1.02, 95% CI 1.01–1.03), for oropharyngeal cancer (HR ¼ 1.02, 95% CI 1.00–1.03) and for laryngeal cancer (HR ¼ 1.03, 95% CI 1.02–1.05). Patients with laryngeal cancer and with educational level of less than or equal to high school had unfavourable OS when compared to those having more than high school education (HR ¼ 2.54, 95% CI 1.01–6.38).

Compared with patients with tumour stage I, patients with tu (HR ¼ 3.10, 95% CI 1.63–5.89) and for laryngeal cancer (HR ¼ 2.46, 95% CI 1.75–3.48). Compared with never smoking status, cigarette smoking was an unfavourable prognostic factor for cancer of the oropharynx (current smokers, HR ¼ 1.83, 95% CI 1.01–3.36; 20 years of smoking, HR ¼ 2.33, 95% CI 1.15–4.72; >20 cigarette per day, HR ¼ 1.87 95% CI 1.01–3.48). Taking as reference the category never smoking, smoking >20 cigarettes/day was an unfavourable prognostic factor for cancer of the oral cavity (HR ¼ 1.41, 95% CI 1.03–1.92).

Compared with never drinkers, alcohol use was associated with a reduced survival in patients with laryngeal cancer (current drinkers, HR ¼ 1.73, 95% CI 1.16–2.58; _1 drinks per day, HR ¼ 1.72, 95% CI 1.12–2.63; >1 drinks per day HR ¼ 1.61, 95% CI 1.04–2.51.)

The distributions of selected covariates, and the adjusted HRs for HNC mortality are shown in Table 4. At multivariate analysis, increasing age at diagnosis was a negative prognostic factor for cancer of the oropharynx and larynx. Taking as reference the cat-egory college graduates, patients with an education less than high school reported a reduced HNC-specific survival considering HNC overall (high-technical school graduate, HR ¼ 1.48, 95% CI 1.01–2.15; less than high school, HR ¼ 1.45, 95% CI 1.02–2.06). Compared with tumour stage I, tumour stage IV was associated with a reduced HNC-specific survival in all HNC sites except for hypopharynx (oral cavity, HR ¼ 3.42, 95% CI 2.24–5.22; oro-pharynx, HR ¼ 3.97, 95% CI 1.86–8.48; larynx, HR ¼ 4.58, 95% CI 2.69–7.80). Cigarette smoking was not associated with a reduced HNC-specific survival in any of the HNC sites. Compared with never drinkers, alcohol drinking was a prognostic factor for patients with cancer of the larynx (current drinkers, HR ¼ 2.11, 95% CI 1.22–3.66; _1 drinks per day, HR ¼ 2.07, 95% CI 1.17–3.69; >1 drinks per day HR ¼ 1.92, 95% CI 1.10–3.43).

Discussion
We evaluated the 5-year overall and HNC-specific survival in a sample of 4198 HNC patients pooled from five studies including centres in three different countries: Italy, Brazil and Japan. Five-year OS was 51.4% and differed across HNC sites: patients with laryngeal cancer reported the highest overall (63.9%) and HNC-specific (72.3%) 5-year survival while patients with hypopharyngeal cancer reported the lowest overall (35.0%) and HNC-specific (37.1%) 5-year survival. Alcohol consumption is not only associated with an increasing risk of laryngeal cancer [8] but also an increasing risk of death.

These results are consistent with previous studies that investi-gated the OS among HNC sites [2, 3, 18]. A study that investi-gated the trends of the survival in patients with HNC reported in the period between 2002 and 2006, a 5-year relative survival rate of 65.9% for HNC overall. Moreover, the OS was highest among patients with laryngeal cancer (66.8%) and lowest among patients with hypopharyngeal cancer (33.8%) [2]. A recent multicentric study, involving 801 HNC patients (also included in our study representing 19% of the sample) in Italy, reported a 5-year relative...
The role of SES on OS in a HNC population and the relationships between SES and the various clinical, demographic and social habits associated with HNC risk and survival were recently explored in a study conducted in Canada. The authors reported an association between SES and the OS among HNC patients. However, this association was lost after age at diagnosis, gender, TNM stage and smoking and alcohol status were accounted for. In this study, we reported an association between educa-tional level and the OS for patients with laryngeal cancer and an association between educational level and the HNC-specific survival for HNC overall. We did not have information on SES, and used education as a proxy. We also cannot rule out confounding by SES indicators such as income or occupation.

Several epidemiological studies have investigated the association between cigarette smoking and alcohol consumption on survival from HNC, reporting contrasting results [12, 13, 18]. A population-based study conducted in Italy and not included in the current pooled analysis reported an association between smoking and survival from laryngeal cancer, while no effect of al-cohol consumption was found [20]. The same relationship was later explored by larynx subites, reporting cigarette smoking as an independent prognostic factor for the cancer of the endo‐larynx and alcohol consumption as an independent prognostic factor for cancer of the epilarynx [12]. A multicentric study conducted in Italy reported alcohol consumption as predictor of survival in patients with cancer of the larynx [18]. A large population-based study conducted in Ireland found that smoking was a strong predictor of survival in patients with cancer of the oral cavity, pharynx and larynx, and the association was stronger in pa-tients treated with surgery [22]. Another study conducted in Japan found smoking as a predictor of OS but not of the HNC-specific survival for patients with cancer of the oral cavity [19]. Moreover, a study conducted in the United States highlighted the effect of smoking on increasing risk of death in patients with p16-positive and p16-negative oropharyngeal cancer [23].

In this study, we observed an increased risk of overall mortality for smokers with cancer of the oral cavity and oropharynx and for alcohol drinkers with cancer of the hypopharynx and larynx. However, when we restricted the analysis to the specific mortality due to HNC, the only prognostic factor that we found was alcohol consumption for patients with laryngeal cancer. As observed in a multicentric European study that investigated lifestyle habits as prognostic factors in survival of laryngeal and hyopharyngeal can-cer [12], the effect of smoking (and alcohol drinking) on survival may be due to the excessive mortality of heavy smokers and alcohol drinkers due to causes other than HNC. Furthermore, it is possible that current smokers have stopped smoking during follow-up, and this would lead to an underestimation of the true effect of smoking.

Limitations of this study are the lack of information on comor-bidities when investigating the cancer-specific survival, and the lack of information on HPV status when investigating the sur-vival of patients with oropharyngeal cancer. Moreover, we did not have data on patient's behaviour after the diagnosis, which may have affected the overall and specific survival. Despite these limitations, our study has several strengths, including the indi-vidual data pooled study design that led us to a large number of HNC patients from three world regions. Due to the large sample size, we were able to evaluate the survival in HNC subites and to adjust for multiple factors when estimating the prognostic factors for specific HNC subites.

This study showed that cigarette smoking was a prognostic factor of the OS for patients with cancer of the oral cavity and oropharynx, and alcohol drinking was a prognostic factor of the OS and HNC-specific survival for patients with cancer of the larynx. Patients with cancer of the larynx and with low educa-tional level also had an unfavourable prognosis. Additional studies including a large sample of patients that allow the ad‐justment for the main confounders, including comorbidities, and the lifestyle habits after the diagnosis might de-pone and will highlight the differences of HNC subites in terms of lifestyle related prognostic factors.

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Disclosure
The authors have declared no conflicts of interest.
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