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The influence of smoking, age and stage at diagnosis on the survival after larynx, hypopharynx and oral cavity cancers in Europe: the ARCAGE study

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Brief description – “Novelty and Impact”

Head and neck cancer (HNC) is a complex and difficult-to-treat malignancy that leads to severe disabilities and high mortality. We investigated if, after major improvements in diagnosis and therapeutic modalities, HNC survival has increased in Europe, and what are the main determinants of outcome. We found that survival from HNC remains low in Europe and, alongside with late stage at diagnosis, older age at diagnosis and smoking are strong predictors of outcome.

Abstract

Head and neck cancer (HNC) is a preventable malignancy that continues to cause substantial morbidity and mortality worldwide. Using data from the ARCAGE and Rome studies, we investigated the main predictors of survival after larynx, hypopharynx and oral cavity (OC) cancers. We used the Kaplan-Meier method to estimate overall survival, and Cox proportional models to examine the relationship between survival and sociodemographic and clinical characteristics. 604 larynx, 146 hypopharynx and 460 OC cancer cases were included in this study. Over a median follow-up time of 4.6 years, nearly 50% (n=586) of patients died. Five-year survival was 65% for larynx, 55% for OC, and 35% for hypopharynx cancers. In a multivariable analysis, we observed an increased mortality risk among older (≥71 years) vs. younger (≤50 years) patients with larynx/hypopharynx combined (LH) and OC cancers [HR=1.60, 95% CI 1.09–2.37 (LH) and HR=2.10, 95% CI 1.34–3.29 (OC)], current vs. never smokers [HR=2.70, 95% CI 1.42–5.14 (LH) and HR=2.11, 95% CI 1.29–3.46 (OC)], and advanced vs. early stage disease at diagnosis [IV vs. I, HR=2.61, 95% CI 1.78–3.81(LH) and HR=3.22, 95% CI 2.08–4.96 (OC)]. Survival was not associated with sex, alcohol consumption, education, oral health, p16 expression, presence of HPV infection, or body mass index 2 years before cancer diagnosis. Despite advances in diagnosis and therapeutic modalities, survival after HNC remains low in Europe. In addition to the recognized prognostic effect of stage at diagnosis, smoking history and older age at diagnosis are important prognostic indicators for HNC.

Introduction

Head and neck cancer (HNC) is mostly comprised of oral cavity, oropharynx, hypopharynx, and larynx tumors. When taken together, HNC represents the 5th most common malignancy in males in the high-income countries, with a lower incidence among females (male to female ratio varies from 2:1 to 4:1).[1] Over 90% of cases are squamous cell carcinomas.[2] HNC can be cured if the tumor is diagnosed at early stage and limited to the head and neck region. However, prognosis is very poor when HNC is diagnosed at later stages with metastatic or recurrent disease. A decision between aggressive multimodality and function-preserving treatment should be based on patient's health and comorbidities, and on the extent to which therapy may affect the patient's quality of life.[3]

Tobacco exposure (including active and smokeless tobacco use) and alcohol consumption are well-established risk factors for HNC.[4] *Human Papillomavirus (HPV)* infection is an additional independent risk factor for oropharynx cancer. Studies have shown that HPV-related HNC is genetically and biologically different from smoking-associated HNC, with HPV-related HNC demonstrating improved clinical outcomes.[3] HPV positive oropharynx cancer patients commonly have greater survival than HPV negative cases.[5-7] However, the same HPV causal and prognostic associations have not been observed for larynx, hypopharynx, or oral cavity cancer where HPV infections are rare.[8]

Stage at diagnosis has been considered one of the strongest predictors of survival among patients with HNC,[9] whereas the role of smoking and alcohol on survival remains controversial. Robust epidemiological data may help to identify modifiable prognostic factors and guide cancer prevention programs aimed to reduce the burden of HNC worldwide.[10] In this study we focused on the determinants of survival from larynx, hypopharynx, and oral cavity cancers in Europe. A separate study has examined survival from oropharynx cancer including the role of HPV.[11]

Patients and methods

Patients

Data was obtained from 14 centers located in 9 European countries. Thirteen centers were participants of the ARCAGE* case-control study[12] as follows: Czech Republic (Prague), Germany (Bremen), Greece (Athens), Italy (Aviano, Padova, and Turin), Ireland (Dublin), Norway (Oslo), United Kingdom (Glasgow, Manchester, and Newcastle), Spain (Barcelona), and Croatia (Zagreb). The remaining data were obtained from a case-control study in Rome.[13] The recruitment of cases was performed from 2002 to 2005 for the ARCAGE study (n=1,066) and from 2003 to 2011 for the Rome study (n=144). Details of the ARCAGE and Rome projects can be found elsewhere.[12,13]

Cases eligible for inclusion in our study were all patients with a primary squamous cell carcinoma of the larynx, hypopharynx or oral cavity confirmed by histology or cytology. We included the following topography codes from the *International Classification of Diseases for Oncology*, 3rd edition (ICD-O-3)[14]: C320-C32.9 for larynx, C12.9 and C13.0-C13.9 for hypopharynx, and C00.3-C00.9, C02.0-C02.3, C03.0-C03.9, C04.0-C04.9, C05.0, and C06.0-C06.9 for oral cavity cancers. Following a standard protocol, participants underwent an identical questionnaire-based interview within 6 months of diagnosis in order to obtain sociodemographic information, complete lifetime smoking and alcohol histories, dietary habits, dental health and care, and education level attained. Biological samples (blood and/or tumor blocks) were also collected. Data on stage at diagnosis, overall treatment, and clinical outcome were subsequently obtained from population-based registries, medical records, linkage with regional or national death index, as well as doctor's contact. Participants were followed from the date of diagnosis to the date of death, loss to follow-up or end of study (31st December 2011), whichever occurred first. Patient's follow-up was performed once from 2012 to 2015 to obtain last known vital status (alive, death, or lost to follow-up) and date of last contact.

Sociodemographic, clinical and lifestyle variables

The sociodemographic, clinical and lifestyle variables were classified as follows. Age at diagnosis was categorized in 4 groups (≤50, 51–60, 61–70, and ≥71 years). Tumor stage at diagnosis was classified in stage I to IV based on the TNM system of the American Joint Commission on Cancer (AJCC) Staging Manual, 6th edition.[15] Smoking was examined in

*Alcohol-Related Cancers and Genetic Susceptibility in Europe

3 different ways: overall history (never, former or current smokers), duration (never, 1–9, 10–19, 2029, 30–39 and ≥40 years), or intensity (number of pack of cigarettes per year: never, <20, 20–39, 40–59, ≥60). Smokers were individuals who used any tobacco product (estimated based on cigarette equivalents) at least once a week for one year. Alcohol consumption was also examined in 3 ways: overall history (never, former or current drinkers), duration (never, 1–9, 10–19, 20–29, 30–39 and ≥40 years), and intensity (number of drinks per day: <5 or ≥5). Information on overall smoking and alcohol histories were obtained from all centers, whereas Rome did not have information on duration and intensity of these variables. Therefore, overall histories were included in the main models and separate models, excluding Rome cases, waere performed to examine the effect of smoking and alcohol duration and intensity on survival, and were included in the supplementary materials (Table S1).

Education was categorized as level of education attained by the time of diagnosis: primary school, secondary school or university degree. Body mass index (BMI, kg/m^2): was examined using self-reported height and weight 2 years before cancer diagnosis, which decreases the probability that low BMI is secondary to cancer development.[16] BMI was classified according to the World Health Organization into 4 categories: underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9) and obese (≥30.0). Dental care and oral hygiene scores were created and classified as good, moderate, and poor as described elsewhere.[17]

Binary variables were sex (male/female) and the HPV tumor markers HPV16 DNA and p16 protein expression (positive/negative). HPV16 DNA genotyping was done using the type-specific E7 polymerase chain reaction bead-based multiplex assay (TS-E7-MPG, IARC, Lyon, France) as described elsewhere.[17] The qualitative assessment of antigen $p16^{INK4A}$ was performed by immunohistochemistry, using the CINtec Histology kit according to the manufacturer's instructions (www.mtmlabs.com). P16 expression was scored based on the intensity and the proportion of nuclear and cytoplasmic stained cells, and was considered positive when the combined score was equal to 4 or higher. Studies have shown that combined p16 expression and HPV16 DNA testing are needed to predict outcome for HNC.[18] We examined p16 expression alone and combined with HPV16 DNA as follow: p16 (–) DNA (–), p16 (+) DNA (–), p16 (+) DNA (+), and p16 (–) DNA (+). In addition to the variables above, we provided a descriptive analysis on relapse occurrence and overall treatment.

Statistical analyses

We used the Kaplan-Meier method to estimate 2-, 5- and 8-year overall (all-cause) survival, and used the log-rank test to examine differences in survival across strata of each variable. Overall survival is presented by anatomic site and, sample size allowing, by tumor subsite (glottis vs. supraglottis, tongue vs. other regions of the mouth, as well as pyriform sinus and other hypopharynx regions).

Multivariable Cox regression models were used to obtain the hazard ratios (HRs) of death and corresponding 95% confidence intervals (CI). We used the likelihood ratio test as an overall significance test for the association of each independent variable with the hazard ratio of death. We tested the proportional hazard (PH) assumption by examining log-log survival plots, and confirmed the results by using Schoenfeld's global test. The PH assumption was met for all variables in the multivariable models. We included in the multivariable models the variables with *a priori* hypothesized or previously observed associations with survival (sex, age and stage at diagnosis, smoking and alcohol histories, BMI 2 years before diagnosis, education level, and dental care). A separate model was performed to examine the association between HPV tumor markers and survival.

Given the modest number of hypopharynx cases, they were pooled with larynx cases for the multivariable analysis. When we performed separate Cox models, we observed the same pattern of associations for both larynx and hypopharynx cases, but with larger confidence intervals and p-values for hypopharynx cases due to the smaller sample size. Cases from Rome did not provide data on education, BMI pre-diagnosis and oral health. Missing data were handled by including them as "unknown" categories in the multivariable models (omitted in the tables). A complete analysis where missing data were excluded was also conducted, and similar results were obtained. We tested for interactions between tumor sites and each variable and found no significant interaction. Statistical analyses were performed using Stata 14 software (StataCorp, College Station, TX, USA), and a 2-sided p-value of less than 0.05 was considered statistically significant.

Ethics approval

The ARCAGE study was approved by the Ethical Review Board of the International Agency for Research on Cancer (IARC), as well as the respective local boards in the individual participating centers. The Rome study was approved by the ethical committee of Fondazione Policlinico Universitario "A. Gemelli". All participants provided written informed consent for their participation in the study.

Results

A total of 604 (50%) larynx, 146 (12%) hypopharynx and 460 (38%) oral cavity cancer cases were included in this study. The sociodemographic and clinical characteristics of patients are summarized by anatomic site in Table 1. Overall, most of patients were males (82%), ever smokers (91%), and ever drinkers (93%), had a median age at diagnosis of 60 years, and were diagnosed with advanced stage disease (55% stages III or IV vs. 45% stages I or II).

Overall survival

The median follow-up time was 4.6 years. Of 1,210 patients, nearly half (n=586) died over the course of follow-up. Five-year survival was 65% for larynx (95% CI 61.1–69.2), 55% for oral cavity (95% CI 50.1–59.7) and 35% for hypopharynx (95% CI 26.8–42.5) cancers (Tables 2A & 2B, Figure1A). When an adequate sample size was available, survival was also examined by anatomic subsite. Based on the log-rank test, we observed that 5-year survival was higher among patients with glottic vs. supraglottic cancer (77% vs. 58%), and for those with tumor of the tongue vs. other regions of the mouth (63% vs. 50%). There was no evidence of difference in survival between patients with cancer of the pyriform sinus and other hypopharynx regions (Figures 1B-D).

For all anatomic sites, we found strong evidence of an association between worse survival and smoking history (former or current smoker) (Tables 2A & 2B,) or advanced stage disease at diagnosis (Tables 2A & B, Supplementary Figure S1). Among oral cavity cancer patients, we also found associations of lower survival with older age at diagnosis, male sex, lower level of education, and low BMI 2 years before cancer diagnosis). There was no evidence of survival differences by p16 protein expression alone or combined with HPV testing for any cancer site (Table 2A & 2B). Survival did not vary by cancer center or country (data not shown).

Hazard ratio of death

In a multivariable Cox regression analysis, in which all variables were mutually adjusted for, we found, among larynx/hypopharynx cases, an increased risk of death for hypopharynx vs. larynx cancer (HR=2.30, 95% CI 1.79–2.95), older compared to younger patients (≥71 vs. ≤ 50 years, HR=1.60, 95% CI 1.09–2.37), current vs. never smokers (HR=2.70, 95% CI 1.42–5.14) and advanced vs. early stage disease at diagnosis (IV vs. I, HR=2.61, 95% CI 1.78–3.81). Likewise, among oral cavity cancer patients, we observed

an increased risk of death for older compared to younger patients (≥71 vs. ≤ 50 years, HR=2.10, 95% CI, HR=1.34–3.29; and 61–70 vs. ≤ 50 years, HR=1.67, 95% CI 1.13–2.47), current vs. never smoker (HR=2.11, 95% CI 1.29–3.46), and for those with advanced vs. early stage at diagnosis (IV vs. I, HR=3.22, 95% CI 2.08–4.96) (Table 3). We did not find significant associations between the risk of death and sex, dental care or BMI 2 years pre-diagnosis.

In separate analyses, when we used the number of packs of cigarettes smoked per year or duration of smoking instead of overall smoking history (Rome cases excluded), similarly strong associations were found. For instance, larynx/hypopharynx patients who smoked ≥20 cigarette pack years had approximately 3 times higher risk of death than never smokers. Likewise, for oral cavity cancer, patients who smoked ≥20 cigarette pack years had a risk of death about 2.5 times higher than never smokers. (Supplementary Table S1) When we examined alcohol duration and intensity, we also did not find evidence of an association between the risk of death and alcohol consumption (Supplementary Table S1). There was no evidence of an association between the risk of death and p16 expression, whether examined alone or combined with HPV testing (Figure 2, Supplementary Table S2).

Descriptive analysis

Data on relapse was available for approximately 80% of cases. Out of 973 patients, 341 (35%) relapsed. Higher incidence of relapse was observed among patients with hypopharynx (46%), followed by oral cavity (38%) and larynx (30%) cancers (p=0.002). After excluding cases to whom relapse occurred less than 90 days from diagnosis (n=49), we observed that the majority of patients (n=194, 72%) relapsed within 2 years of HNC diagnosis, whereas 19% (n=52) and 9% (n=25) relapsed within >2 to 5 years and >5 to 10 years respectively (Supplementary Figure S2). Time to relapse did not differ significantly by anatomic site.

Overall information on type of treatment was available for approximately 97% of cases. Surgery was performed in most of patients (66%), alone (34%) or combined with radiotherapy (28%), chemotherapy (1%), or both (11%). About 12% of patients received radiotherapy alone, 10% received chemotherapy and radiotherapy, and 1% received chemotherapy alone. For about 2% of patients no type of treatment was reported.

Discussion

Our results reveal that survival from head and neck cancer remains low in Europe. Except for patients with tumors of the glottis, 8-year survival was lower than 50% for all tumor sites and subsites. In the multivariable models, the main predictors of survival were age at diagnosis, stage at diagnosis, smoking history, and anatomic site.

Age at diagnosis is often considered an independent predictor of outcome for many types of cancer.[19,20] The influence of age on HNC survival remains controversial. In a recent review, which included surgical, radiation-alone, and chemoradiation studies from 1980 to 2012, the authors concluded that even though elderly patients may experience higher treatment-related toxicities than their younger counterparts, there was not sufficient evidence that survival is worse among older than younger patients (the majority of the studies investigated overall rather than disease-free or cancer-specific survival).[21] Another study which use data from the Surveillance Epidemiology and End Results (SEER) program in the United States (US) and estimated overall survival of patients diagnosed with larynx, tongue or tonsil cancer between 1988 and 1998, supported these findings.[22]

In contrast, our findings of increased risk of death among older patients (≥71 years for larynx/hypopharynx and ≥61 years for oral cavity cancers) support the results of several population-based studies in Europe and in the US. For instance, a European study used data from 15 French cancer registries on patients diagnosed with HNC between 1989 and 1997. The authors found that relative survival (which accounts for competing causes of death) was consistently lower for elderly compared to younger patients. The excess mortality among patients aged>75 years was apparent during the first 3 months and after 3 years of diagnosis, with no significant influence of age between 1 and 3 years after diagnosis.[23] Likewise, in a later European study on HNC, relative survival was lower among elderly (≥ 75 years) vs. younger patients diagnosed from 1999 to 2007.[9] In the US, a study from a large university-based cancer registry used data from 1990 to 2005 and found that, after adjusting for potential confounders, patients with HNC aged ≥70 years at diagnosis had a risk of death about twice as high as that of patients younger than 70 years.[24] Notably, the authors showed that when older patients with advanced disease (stage at diagnosis III–IV) were treated with multimodality therapy, 5-year overall survival was close to that of younger patients who received similar therapeutic management. However, older patients who received single-modality treatment had dramatically lower 5-year survival than their younger counterparts. Older age is commonly associated with moderate to severe

comorbidities, which may diminish the patient's ability to tolerate surgery and intensive cancer adjuvant treatment, such as radiotherapy and/or chemotherapy.[10] Comorbidities such as cardiovascular and pulmonary diseases in HNC patients are mostly secondary to smoking and excessive alcohol use. In addition, advanced age is associated with a decline in immune function,[25-27] which may not only facilitate cancer progression, but also weaken the host immune response against cancer.[10] Nonetheless, studies suggest that, since cancer is the main cause of death among elderly patients with advanced HNC, the competing causes of death likely contribute to a small fraction of the lower survival observed among these patients.[24] The main challenge in the treatment of elderly patients with HNC is to decide for which patients the benefit of intensive multimodality therapy compensates the risk of treatment toxicity.

Stage at diagnosis is widely considered a main determinant of cancer survival and this is also true for HNC.[9] Our results showed that even with the advance on diagnosis procedures observed in the last decades, the majority of patients (55%) with HNC are still diagnosed with advanced disease (stage III–IV) in Europe. This proportion is close to the EUROCARE-5 study,[9] which used data from 29 European countries on patients diagnosed from 1999 through 2007. The authors emphasized that over 54% of patients were diagnosed with regional or metastatic disease. We found that the risk of death was approximately 2 or 3 times greater among patients with stage III or IV, respectively, than those with stage I at diagnosis. While HNC can be often cured when diagnosed at early stage, late stage disease may be untreatable or involve aggressive multimodality treatment that often leads to severe physical and psychological disabilities. It has been reported that HNC have the highest risk of disability and work quitting, together with central nervous system and hematologic malignancies[28]

We observed a strong association between smoking and survival. This association was significant for all investigated variables (overall smoking history, duration, and intensity) and highlights the importance of intensifying tobacco prevention and control in Europe. According to the World Health Organization, smoking kills closely 6 million people per year, more than HIV/AIDS, malaria and tuberculosis combined. It has been estimated that this number can increase to over 8 million people by 2030 if more immediate and severe actions are not taken.[29] While some previous studies had shown negative[30,31] or limited[32,33] association between smoking and HNC survival, our findings support a large population-based study conducted in Ireland which revealed that smoking at diagnosis was associated with worse survival.[34] The authors highlighted that this association was

stronger among patients who had surgical treatment for their HNC, and neither chemotherapy nor radiotherapy influenced the effect of smoking on survival. One relevant question in the clinical setting is whether smoking cessation after cancer diagnosis can improve prognosis of HNC, for instance decreasing treatment complications and the risk of relapse or second primary malignancy.[35] Post-treatment smoking history was not available in our study.

While our results support the influence of smoking on survival from HNC, we did not find the same association regarding alcohol consumption and survival when we examined overall alcohol history, duration or intensity. Our findings differ from a US study[36] which found that alcohol consumption pre- and post-diagnosis adversely affected HNC survival, and highlighted the need for aggressive interventions to help patients to abstain from or decrease alcohol intake. In another US study,[37] which enrolled over 1,000 patients with HNC, about 17% of patients had secondary tumors. Strikingly, alcohol consumption combined with smoking after diagnosis was found to significantly increase the risk of secondary tumors among these patients. More studies in Europe are needed to investigate the association between alcohol pre- and post-diagnosis and HNC outcomes.

In our study, HNC prognosis varied significantly by anatomic site, with better survival for larynx, intermediate for oral cavity, and worse for hypopharynx cancer patients. These results are consistent with previous survival studies in Europe. For example, the EUROCARE II study,[38] which used data from 17 countries on patients diagnosed from 1985 to 1989, revealed that overall, 5-year relative survival was approximately 63% for larynx, 41% for oral cavity, and 22% for hypopharynx cancer, with wide geographic variations (higher survival in Western than Eastern European countries). The authors suggested that possible reasons for the observed survival disparities are late diagnosis, late referral to treatment, and lack of access to effective treatment. The subsequent EUROCARE-5 study[9] showed that 5-year relative survival after larynx cancer has not improved over time (from 1999–2001 to 2005–2007), whereas survival improved by 3–5% (absolute difference) for oral cavity, oropharynx, and hypopharynx. However, 5-year relative survival was still low: 25% for hypopharynx and 45% for oral cavity cancer patients. Although our results are not directly comparable, the same survival pattern was observed in our cohort of patients, suggesting no or little improvement in the last few decades, despite progresses in diagnosis procedures and therapeutic management. This finding is concerning and emphasizes the need for increased healthcare policy aimed at decreasing

modifiable risk factors (such as smoking and alcohol consumption) for HNC occurrence in Europe.

Curative treatment for HNC is complex and often negatively impacts patient's quality of life (e.g. causing difficulty to speak, breath, swallow, as well as facial deformity). Advancements in treatment such as new surgical techniques, the use of concurrent or alternating chemoradiation, hyperfractionated or accelerated radiotherapy, and more recently immunotherapy, may improve HNC survival and reduce the burden of complications secondary to treatment.[39] However, improvement in HNC outcomes have been disappointing. Despite treatment advances, larynx cancer is one of the few types of cancer in which survival has recently decreased in the US (from 66% during 1975–1977 and 1987–1989 to 63% during 2005–2011).[40] It has been postulated that the declining survival trends are due to changes in treatment toward a nonsurgical (organ preservation) approach.[41,42]

For hypopharynx cancer, a recent population-based study[43] using SEER data showed evidence of increasing survival trends since 1990: 5-year overall survival improved from 38% during 1973–1989 to 41% during 1990–2003. Through the study period, there was a trend toward reduced surgical treatment and increased use of radiation-only therapy. In contrast to what has been observed for larynx cancer in the US, this study suggests that organ preservation may have a survival benefit for hypopharynx cancer patients. For oral cavity cancer, surgery remains the first-line treatment, while[44] radiotherapy and lymph node resection are usually performed for advanced stage disease or for those patients considered ineligible for surgical interventions.

It has been recognized that approximately 50% of patients with HNC have substantial weight loss at diagnosis and just before start of therapy in consequence of cancer symptoms (e.g. dysphagia, odynophagia, and anorexia),[45] and this has been shown to negatively impact survival.[46] Therefore, we aimed to investigate whether BMI 2 years before diagnosis also influence survival after HNC. After multiple adjustments, we did not observe a significant association between the risk of death and underweight, which may be explained by the small number of patients in this category (fewer than 3.5%). Likewise, overweight or obesity pre-diagnosis was not found to impact survival among our patients.

Finally, when tumor samples were available, we evaluated whether p16 expression alone or associated with HPV16 testing predicts prognosis for non-oropharynx cancers. P16 is a tumor suppressor gene considered a good proxy for HPV infection in tumors.[3]

Our results support the lack of an association between survival and p16 overexpression examined alone, as reported by other authors.[47,48] We also did not find any association with survival when p16 was considered with HPV DNA testing. It is possible that, in our study, the small number of HNC cases that were both HPV DNA and p16 positive have contributed for the negative association we observed. Further studies to investigate the prognostic role of these markers on non-oropharynx cancer outcomes are warranted.

Our study has several limitations. Since the ARCAGE study was initially designed to look at risk factors of head and neck cancer, collection of clinical data such as detailed treatment approach and relapse (including dates of treatment and relapse) were restricted. Therefore it was not possible to investigate the impact of treatment modality on survival or relapse. We used self-reported weight and height 2 years before diagnosis, which may be subject to inaccuracy and bias. However, previous studies have shown high correlation ($r>0.9$) between self-reported and measured height, weight and BMI. [49,50] Overall, data were missing on stage at diagnosis in about 21% of cases. However, the strong association we found between stage at diagnosis and survival supports previous studies and emphasizes the impact of late diagnosis on HNC prognosis. Although Rome did not have information on certain variables, the data provided by this center were valuable and the associations we found remained even when these cases were excluded from the analyses. We also lacked information on comorbidities, performance status, and treatment complications. Although these data would likely have contributed additional findings, predictors of HNC outcome such as smoking, stage and age at diagnosis are of paramount importance and were clearly demonstrated in our study. In addition, the strengths of the ARCAGE study includes a standard protocol, data from several European centers with detailed information on smoking and alcohol histories, tumor histological or cytological confirmation for all patients, as well as blood and tumor samples for several cases.

In summary, HNC is a complex malignancy that involves vital anatomic structures, which make it difficult to treat. Surprisingly, despite the advances in diagnosis and therapeutic modalities, survival after HNC remains low in Europe. Most patients continue to be diagnosed with disease at advanced stage, which often requires aggressive treatment and may lead to substantial disabilities and psychological disorders, reducing quality of life among survivors. The association between older age and inferior survival suggests that treatment should be personalized based on patients' comorbidities and tolerability. Importantly, public health efforts in Europe should focus on primary prevention to deter the initiation of tobacco use, promote smoking cessation, and prevent excessive

alcohol consumption. In addition, secondary prevention to detect HNC at an earlier stage is crucial.

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Author contributions

RA had full access to all of the data and performed the statistical analyses. DA designed and coordinated survival data collection, managed and curated the ARCAGE database. PB coordinated the ARCAGE study and advised and reviewed the statistical analyses. RA led the writing and review of the manuscript. All authors participated in the interpretation of data and critical review of the manuscript. All authors read and approved the final manuscript.

Conflict of interest

We declare no conflict of interests.

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602
603 **Table 1: Sociodemographic and clinical characteristics of patients with larynx, hypopharynx, and oral cavity cancers**
604

Description	Larynx, *N* (%)	Hypopharynx, *N* (%)	Oral cavity *N* (%)
Total= 1,210	604 (49.9)	146 (12.1)	460 (38.0)
Age at diagnosis, years			
Median (IQR)	62 (55-69)	58 (52-64)	59 (52-68)
≤50	75 (12.4)	31 (21.2)	97 (21.1)
51–60	195 (32.2)	54 (37.0)	165 (35.9)
61–70	219 (36.3)	44 (30.1)	119 (25.9)
≥71	111 (18.4)	17 (11.6)	79 (17.2)
Unknown	4 (0.7)	0	0
Sex			
Male	526 (87.1)	131 (89.7)	329 (71.5)
Female	75 (12.4)	15 (10.3)	131 (28.5)
Unknown	3 (0.5)	0	0
Smoking history			
Never	35 (5.8)	10 (6.9)	69 (15.0)
Former	231 (38.2)	36 (24.6)	107 (23.3)
Current	335 (55.5)	100 (68.5)	284 (61.7)
Unknown	3 (0.5)	0	0
Alcohol use history			
Never	45 (7.4)	0 (0)	39 (8.5)
Former	67 (11.1)	24 (16.4)	60 (13.0)
Current	482 (79.8)	122 (83.6)	362 (78.5)
Unknown	10 (1.7)	0	0
Stage at diagnosis			
I	131 (21.7)	8 (5.5)	86 (18.7)
II	95 (15.7)	12 (8.2)	93 (20.2)
III	111 (18.4)	29 (19.9)	47 (10.2)
IV	140 (23.2)	66 (45.2)	134 (19.1)
Unknown	127 (21.0)	31 (21.2)	100 (21.7)
Level of education*			
Finished primary school	207 (34.3)	47 (32.2)	140 (30.4)
Finished secondary school	263 (43.5)	89 (60.0)	270 (58.7)
University degree	25 (4.1)	4 (2.7)	20 (4.4)
Unknown	109 (18.1)	6 (4.1)	30 (6.5)
BMI 2 years pre-diagnosis (kg/m^2)*			
Underweight (<18.5)	6 (1.0)	4 (2.7)	14 (3.1)
Normal weight (18.5–24.9)	223 (36.9)	66 (45.2)	193 (42.0)
Overweight (25.0–29.9)	181 (30.0)	49 (33.6)	151 (32.8)
Obesity (≥30)	79 (13.1)	18 (12.3)	54 (11.7)
Unknown	115 (19.0)	9 (6.2)	48 (10.4)
Dental care*			
Good	85 (14.1)	27 (18.5)	79 (17.2)
Moderate	397 (65.7)	106 (72.6)	338 (73.5)
Poor	9 (1.5)	5 (3.4)	9 (2.0)
Unknown	109 (18.7)	8 (5.5)	34 (7.4)
Oral Hygiene*			
Good	197 (32.6)	72 (49.3)	207 (45.0)
Moderate	108 (17.9)	22 (15.1)	84 (18.3)
Poor	190 (31.5)	46 (31.5)	140 (30.4)
Unknown	113 (18.0)	6 (4.1)	29 (6.3)
Subset of patients with available data on HPV tumor markers*			
p16 expression (n=561)			
Negative	237 (78.7)	56 (88.9)	169 (85.8)
Positive	64 (21.3)	7 (11.1)	28 (14.2)
HPV16 DNA (n=715)			
Negative	280 (72.7)	49 (64.5)	186 (73.2)

Description	Larynx, *N* (%)	Hypopharynx, *N* (%)	Oral cavity *N* (%)
Positive	105 (27.3)	27 (35.5)	68 (26.8)
p16/HPV16 DNA status (n=535)			
p16 (–) DNA (–)	164 (56.8)	29 (50.0)	116 (61.7)
p16 (+) DNA (–)	35 (12.1)	4 (6.9)	18 (9.6)
p16 (+) DNA (+)	27 (9.3)	3 (5.2)	7 (3.7)
p16 (–) DNA (+)	63 (21.8)	22 (37.9)	47 (25.0)

Abbreviations: HPV, Human Papillomavirus; p16, protein expression; BMI, body mass index. *Cases from Rome did not provide data on education, BMI, and oral health (dental care and oral hygiene).

605

606

607 **Table 2A: Two-, 5- and 8-year overall survival after larynx and hypopharynx cancers in Europe**

	2-y survival (%) (95% CI)	5-y survival (%) (95% CI)	8-y survival (%) (95% CI)	p-value‡
Overall	76.0 (72.7-79.0)	59.0 (55.2-62.7)	39.5 (33.7-45.3)	
Larynx	81.3 (77.8-84.3)	65.3 (61.1-69.2)	43.5 (36.4-50.4)	
Hypopharynx	55.3 (46.7-63.0)	34.6 (26.8-42.5)	23.8 (16.4-32.0)	<0.0001
Age at diagnosis, years				
≤50	75.9 (66.2-83.2)	55.0 (44.6-64.2)	44.1 (33.7-54.0)	
51–60	76.4 (70.4-81.4)	63.0 (56.3-68.9)	41.9 (31.1-52.2)	
61–70	76.6 (70.8-81.4)	61.0 (54.4-66.9)	40.9 (30.6-51.0)	
≥71	74.2 (65.4-81.1)	51.2 (41.5-60.0)	28.5 (16.7-41.4)	0.2071
Sex				
Male	75.5 (71.9-78.7)	59.4 (55.3-63.2)	40.0 (33.8-46.2)	
Female	80.1 (69.6-87.4)	57.3 (45.2-67.7)	36.3 (21.0-51.8)	0.9185
Smoking history				
Never	85.6 (70.8-93.3)	77.7 (61.4-87.8)	72.1 (55.2-83.6)	
Former	79.8 (74.2-84.2)	58.1 (51.4-64.3)	37.0 (25.9-48.0)	
Current	72.7 (68.1-76.8)	57.5 (52.5-62.1)	37.4 (30.1-44.7)	0.0111
Alcohol use history				
Never	89.1 (73.3-95.8)	66.7 (47.7-80.1)	.*	
Former	73.0 (62.5-81.1)	57.2 (46.0-66.9)	46.8 (34.0-58.6)	
Current	75.5 (71.8-78.9)	58.8 (54.6-62.8)	38.3 (31.7-44.7)	0.4631
Stage at diagnosis				
I	89.4 (82.7-93.6)	78.9 (70.7-85.0)	64.7 (50.2-75.9)	
II	83.0 (74.0-89.1)	60.5 (50.0-70.0)	43.9 (31.6-55.5)	
III	77.3 (68.8-83.8)	61.7 (52.2-69.9)	26.6 (9.50-47.5)	
IV	63.5 (56.3-69.8)	43.7 (36.4-50.8)	22.9 (13.0-34.5)	<0.0001
Level of education				
Finished primary school	74.5 (68.4-79.6)	58.1 (51.4-64.1)	34.7 (25.7-43.8)	
Finished secondary school	76.7 (71.8-80.8)	61.5 (56.1-66.5)	45.6 (38.3-52.7)	
University degree	74.2 (53.3-86.8)	58.1 (37.0-74.3)	29.0 (2.0-67.7)	0.2775
BMI 2 years pre-diagnosis (kg/m²				
Underweight (<18.5)	53.3 (17.7-79.6)	26.7 (4.1-57.9)	.*	
Normal weight (18.524.9)	74.3 (68.7-79.0)	57.5 (51.4-63.1)	35.2 (27.1-43.4)	
Overweight (2529.9)	80.5 (74.6-85.2)	64.2 (57.4-70.3)	52.9 (44.4-60.7)	
Obesity (≥30)	72.4 (62.1-80.3)	61.1 (50.4-70.2)	29.3 (8.7-54.1)	0.0033
Dental care				
Good	82.6 (74.1-88.5)	65.0 (55.2-73.2)	53.8 (43.4-63.1)	
Moderate	74.4 (70.2-78.1)	58.9 (54.2-63.2)	37.1 (29.5-44.7)	
Poor	64.3 (34.3-83.3)	50.0 (22.9-72.2)	.*	0.1878
Oral Hygiene				
Good	73.9 (68.1-78.9)	60.7 (54.4-66.4)	43.5 (34.4-52.1)	
Moderate	77.3 (68.6-83.8)	65.2 (55.8-73.1)	36.7 (21.7-51.9)	
Poor	76.9 (70.8-81.9)	56.4 (49.6-62.7)	40.5 (32.7-48.8)	0.3682
p16 expression				
Negative	78.2 (72.9-82.6)	58.7 (52.4-64.4)	36.9 (27.8-46.0)	
Positive	80.8 (69.2-88.4)	59.3 (46.1-70.3)	37.1 (19.2-55.2)	0.7634
p16/HPV16 DNA				
p16 (–) DNA (–)	80.2 (73.6-85.3)	63.5 (55.6-70.3)	40.0 (27.1-52.5)	
p16 (+) DNA (–)	78.1 (60.8-88.4)	51.8 (33.3-67.5)	36.1 (13.9-59.1)	
p16 (+) DNA (+)	83.1 (64.0-92.6)	68.6 (48.3-82.3)	38.4 (12.8-64.0)	
p16 (–) DNA (+)	71.0 (59.9-79.5)	49.6 (38.2-59.9)	27.6 (14.9-42.0)	0.1755

Abbreviations: BMI, body mass index; HPV, Human Papillomavirus; p16, protein 16; CI, confidence interval;. ‡Log-rank test p-value. *Could not be assessed.

608

609 **Table 2B: Two-, 5- and 8-year overall survival after oral cavity cancer in Europe** (table was not changed)

	2-y survival (%) (95% CI)	5-y survival (%) (95% CI)	8-y survival (%) (95% CI)	p-value‡
Overall	72.7 (68.2-76.6)	55.0 (50.1-59.7)	30.3 (23.4-37.4)	
Age at diagnosis, years				
≤50	76.2 (66.2-83.7)	60.7 (49.9-69.9)	42.8 (28.4-56.4)	
51–60	76.8 (69.3-82.7)	58.6 (50.3-66.0)	42.4 (32.0-52.5)	
61–70	63.9 (54.2-72.1)	46.8 (37.2-55.9)	23.3 (12.2-36.3)	
≥71	72.6 (60.4-81.6)	52.1 (39.5-63.4)	11.5 (2.8-27.0)	0.0076
Sex				
Male	71.5 (66.0-76.2)	52.3 (46.4-57.8)	27.0 (19.9-34.6)	
Female	75.7 (67.1-82.3)	61.6 (52.3-69.6)	35.8 (17.0-55.2)	0.0474
Smoking history				
Never	82.6 (70.7-89.9)	69.8 (56.8-79.6)	.*	
Former	75.1 (65.4-82.5)	58.1 (47.4-67.4)	29.5 (15.2-45.4)	
Current	69.4 (63.5-74.6)	50.3 (44.0-56.2)	26.7 (19.3-34.6)	0.0211
Alcohol use history				
Never	72.1 (54.4-83.9)	57.6 (39.7-71.9)	43.5 (25.8-59.9)	
Former	80.8 (68.0-88.9)	68.3 (54.4-78.7)	39.9 (23.3-56.1)	
Current	71.3 (66.2-75.9)	52.5 (46.9-57.7)	29.3 (22.1-37.0)	0.4431
Stage at diagnosis				
I	89.3 (80.4-94.3)	78.4 (68.0-85.8)	57.6 (43.0-69.7)	
II	79.7 (69.4-86.9)	63.9 (52.6-73.2)	33.3 (18.0-49.5)	
III	72.5 (56.6-83.3)	54.5 (38.2-68.3)	19.5 (1.91-50.9)	
IV	60.6 (51.2-68.8)	38.1 (29.2-46.9)	7.4 (0.8-24.7)	<0.0001
Level of education				
Finished primary school	69.3 (60.3-76.6)	48.3 (39.1-56.8)	25.7 (15.2-37.5)	
Finished secondary school	75.2 (69.5-80.0)	58.9 (52.6-64.6)	32.2 (23.5-41.3)	
University degree	83.3 (56.8-94.3)	61.1 (35.3-79.2)	50.9 (23.6-73.0)	0.0175
BMI 2 years pre-diagnosis (kg/m^2)				
Underweight (<18.5)	54.5 (25.4-76.5)	39.0 (14.3-63.3)	.*	
Normal (18.5–24.9)	74.6 (67.7-80.3)	54.3 (46.8-61.2)	29.5 (19.4-40.3)	
Overweight (2529.9)	77.9 (70.2-83.8)	63.1 (54.6-70.4)	34.8 (23.7-46.1)	
Obese (≥30)	72.0 (57.4-82.4)	51.9 (37.3-64.6)	19.9 (2.0-51.5)	0.3210
Dental care				
Good	79.5 (68.7-86.9)	65.4 (53.7-74.8)	38.9 (20.7-56.8)	
Moderate	72.8 (67.6-77.4)	54.1 (48.4-59.5)	29.0 (21.6-36.8)	
Poor	74.1 (28.9-93.0)	44.4 (10.4-74.8)	.*	0.0837
Oral Hygiene				
Good	74.5 (67.8-80.0)	59.7 (52.5-66.2)	36.8 (26.8-46.8)	
Moderate	71.8 (60.4-80.5)	46.3 (34.8-57.0)	22.4 (9.9-37.9)	
Poor	73.8 (65.2-80.6)	55.2(46.0-63.4)	26.2 (6.6-39.7)	0.1046
p16 expression				
Negative	68.8 (60.8-75.5)	49.4 (41.0-57.3)	27.7 (15.0-41.9)	
Positive	70.1 (49.0-83.8)	66.2 (45.0-80.8)	.*	0.7036
p16/HPV16 DNA				
p16 (–) DNA (–)	69.2 (59.3-77.2)	49.4 (39.1-59.0)	21.8 (6.6-42.7)	
p16 (+) DNA (–)	66.7 (40.4-83.4)	61.1 (35.3-79.2)	.*	
p16 (+) DNA (+)	64.3 (15.2-90.2)	64.3 (15.2-90.2)	.*	
p16 (–) DNA (+)	72.8 (57.1-83.6)	51.6 (35.9-65.2)	51.6 (35.9-65.2)	0.7821

Abbreviations: BMI, body mass index; HPV, Human Papilloma virus; p16, protein 16; CI, confidence interval. ‡Log-rank test p-value. *Could not be assessed.

610

611 **Table 3: Hazard ratios of death after larynx and hypopharynx (combined) and oral cavity cancers in Europe**

	Larynx/hypopharynx		Oral cavity	
	Multivariable HR (95% CI)*	**p-value‡**	**Multivariable HR (95%CI)***	**p-value‡**
Age at diagnosis, years				
≤50	Reference		Reference	
51–60	1.01 (0.72-1.43)		1.10 (0.75-1.60)	
61–70	1.19 (0.84-1.67)		1.65 (1.12-2.44)	
≥71	1.61 (1.09-2.38)	0.0158	2.12 (1.35-3.33)	0.0012
Sex				
Male	0.96 (0.67-1.37)		1.42 (0.99-2.02)	
Female	Reference	0.8091	Reference	0.0474
Smoking history				
Never	Reference		Reference	
Former	1.87 (0.98-3.55)		1.15 (0.65-2.02)	
Current	2.67 (1.40-5.08)	0.0010	2.16 (1.32-3.54)	0.0002
Alcohol use history				
Never	Reference		Reference	
Former	1.20 (0.62-2.30)		0.72 (0.37-1.37)	
Current	1.22 (0.69-2.17)	0.9083	0.75 (0.43-1.31)	0.5753
Stage at diagnosis				
I	Reference		Reference	
II	1.77 (1.15-2.72)		1.52 (0.94-2.47)	
III	1.87 (1.23-2.86)		2.13 (1.24-3.67)	
IV	2.60 (1.78-3.79)	<0.0001	3.17 (2.05-4.89)	<0.0001
Education				
Primary school	0.93 (0.51-1.72)		1.10 (0.52-2.35)	
Secondary school	0.73 (0.40-1.34)		0.85 (0.41-1.78)	
University degree	Reference	0.2069	Reference	0.2208
BMI 2 years pre-diagnosis (kg/m^2)				
Underweight (<18.5)	1.64 (0.75-3.60)		1.83 (0.84-4.00)	
Normal (18.5–24.9)	Reference		Reference	
Overweight (25.0–29.9)	0.75 (0.58-0.98)		0.98 (0.72-1.34)	
Obese (≥30)	1.09 (0.78-1.52)	0.0970	1.41 (0.92-2.18)	0.0592
Tumor site				
Larynx	Reference		N/A	
Hypopharynx	2.29 (1.79-2.94)	<0.0001		

Abbreviation: BMI, body mass index; HR=hazard ratio of death; CI=confidence interval. *Additionally adjusted for year of diagnosis. ‡Likelihood ratio test.

612

Modified supplementary Tables S1 and S2

Table S1: Hazard ratios of death after larynx, hypopharynx, and oral cavity cancers using smoking and drinking duration or intensity.[&]

	Larynx/hypopharynx		Oral cavity	
	Multivariable HR[£] (95% CI)	p-value[†]	Multivariable HR[£] (95% CI)	p-value[†]
Smoking duration, years				
Never smokers	Reference		Reference	
1–9	4.14 (1.13-15.3)		0.55 (0.16-1.89)	
10–19	3.53 (1.28-9.74)		1.35 (0.60-3.05)	
20–29	1.93 (0.78-4.81)		1.45 (0.78-2.72)	
30–39	2.88 (1.22-6.78)		2.09 (1.21-3.63)	
≥40	3.98 (1.70-9.34)	0.0006	2.92 (1.70-5.02)	<0.0001
Smoking intensity, pack/years				
Never smokers	Reference		Reference	
<20	2.67 (1.10-6.48)		1.61 (0.93 -2.82)	
20–39	3.12 (1.33-7.32)		2.53 (1.47-4.34)	
40–59	3.69 (1.56-8.72)		2.28 (1.28-4.07)	
≥60	3.37 (1.41-8.09)	0.0082	2.47 (1.34-4.59)	0.0156
Drinking duration, years				
Never drinkers	Reference		Reference	
1–9	1.15 (0.30-4.36)		.*	
10–19	1.44 (0.54-3.82)		0.57 (0.26-1.27)	
20–29	1.31 (0.60-2.84)		0.62 (0.32-1.21)	
30–39	1.32 (0.63-2.74)		0.71 (0.39-1.33)	
≥40	1.43 (0.70-2.94)	0.5036	0.80 (0.44-1.47)	0.0167
Drinking intensity, drinks/day				
<5 drinks per day	Reference		Reference	
≥ 5 drinks per day	0.97 (0.74-1.27)	0.0655	1.02 (0.74-1.42)	0.8886

[&]Cases from Rome were excluded due to lack of data. Missing information from other centers: smoking duration: larynx/hypopharynx (LH)=4, oral cancer (OC)=3; smoking intensity: LH=6, OC=4. ; drinking duration: LH =4, OC=2; drinking intensity, LH=8, OC=5. [£]Adjusted for sex, age and stage at diagnosis, education, year of diagnosis, and tumor site. [†]Likelihood ratio test. *Could not be assessed.

Table S2: Hazard ratios of death by p16 expression and HVP16 DNA status after larynx, hypopharynx, and oral cancers in Europe

	Number	Univariable HR* (95% CI)	p-value†	Multivariable HR* (95% CI)	p-value†
p16 expression					
Negative	462	Reference		Reference	
Positive	99	0.91 (0.66-1.25)	0.5699	0.99 (0.72-1.37)	0.9451
p16/HPV16 DNA					
p16 (–) DNA (–)	309	Reference		Reference	
P16 (+) DNA (–)	57	1.13 (0.76-1.68)		1.09 (0.73-1.64)	
P16 (+) DNA (+)	37	0.86 (0.51-1.44)		1.11 (0.65-1.89)	
p16 (–) DNA (+)	132	1.17 (0.88-1.56)	0.5795	1.21 (0.90-1.62)	0.6554

Abbreviations: HPV, Human Papilloma virus; p16, protein expression. *Adjusted by age and stage at diagnosis, sex, smoking history, year of diagnosis, and tumor site. †Likelihood ratio test.

Figure legends

1- Overall survival from head and neck cancers by: A, anatomic site; B, larynx subsite; C, hypopharynx subsite; and D, oral cavity subsite.

2- The hazard ratios of death by HPV tumor markers among patients with larynx, hypopharynx, and oral cavity cancers, 2002–2011, the ARCAGE study