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ORIGINAL ARTICLE

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 = 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 = 1.73, 95% CI 1.16–2.58) and HNC-specific survival (current drinkers HR = 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 = 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 neoplasm has improved over the last decades, but still differs depending on the HNC subsite [2]. For patients with oral cavity, oropharyngeal and hypopharyngeal 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 oropharynx, 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 2002 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 end point 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 end point 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, $\leq$20 cigarettes/day, >20 cigarettes/day) and smoking duration in years (never smokers, $\leq$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, $\leq$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's 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%

Table 1. Characteristics of 4198 cases of head and neck cancer from five studies participating in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium, according to tumour site

Study centre	Recruitment period	Oral cavity		Oropharynx		Hypopharynx		Larynx		OC, OP, HP NOS		Total	
		n	%[a]	*n*	%[a]	*n*	%[a]	*n*	%[a]	*n*	%	*n*	%[b]
Milan, Italy	2002–2009	31	19.9	9	5.8	8	5.1	108	69.2	5	3.1	161	3.8
Rome, Italy	2002–2014	88	17.9	84	17.1	23	4.7	297	60.4	6	1.2	498	11.9
Western Europe	2002–2005	121	34.9	82	23.6	30	8.6	114	32.9	6	1.7	353	8.4
Aviano	2002–2005	46	38.0	34	28.1	9	7.4	32	26.4	2	1.6	123	2.9
Padua	2002–2005	25	21.6	26	22.4	14	12.1	51	44.0	1	0.9	117	2.8
Turin	2003–2005	50	45.5	22	20.0	7	6.4	31	28.2	3	2.7	113	2.7
Sao Paulo, Brazil	2002–2014	1.017	38.3	610	23.0	268	10.1	762	28.7	235	8.1	2.892	68.9
Japan	2001–2005	147	50.0	49	16.7	47	16.0	51	17.3	0	0.0	294	7.0
Total		1.404	35.6	834	21.1	376	9.5	1.332	33.8	252	6.0	4.198	100.0

[a]Row percentages were calculated excluding OC, OP, HP NOS. [b]Column percentages.
OC, oral cavity; OP, oropharynx; HP, hypopharynx; NOS, not otherwise specified.

Table 2. Median survival time and number of deaths by tumour site and study centre

	n	Follow-up time (months)			Deaths		Deaths from HNC	
		Median	1Q	3Q	*n*	%	*n*	%[a]
Tumour site								
Oral cavity	1.404	24	11	58	635	45.2	476	35.3
Oropharynx	834	18	9	51	446	53.5	352	43.7
Hypopharynx	376	20	9	48	226	60.1	168	48.3
Larynx	1.332	42	16	75	482	36.2	304	23.2
OC, OP, HP NOS	252	27	11	71	135	53.6	108	43.4
Study centre								
Milan, Italy	161	59	26	81	80	49.7	41	25.5
Rome, Italy	498	48	18	85	200	40.6	103	21.0
Western Europe								
Aviano	123	87	38	99	51	41.5	40	33.1
Padua	117	61	17	97	67	57.3	50	42.7
Turin	113	79	18	100	64	56.6	48	42.5
Sao Paulo, Brazil	2.892	20	10	45	1.367	47.3	1.126	39.4
Japan	294	60	40	75	95	32.3	na	
Total	4.198	27	11	63	1.924	45.8	1.408	34.7

[a]Percentages were calculated excluding missing values.
HNC, head and neck cancer; OC, oral cavity; OP, oropharynx; HP, hypopharynx; NOS, not otherwise specified; na, not available; 1Q, first quartile; 3Q, third quartile.

from Italy (Milan, Rome, Aviano, Turin, Padua) and the remaining 7.0% from Japan. Disease location was oral cavity in 1404 (35.6%) patients, oropharynx in 834 (21.1%) patients, hypopharynx in 376 (9.5%) patients, larynx in 1332 (33.8%) 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 hypopharynx and 36.2% for larynx.

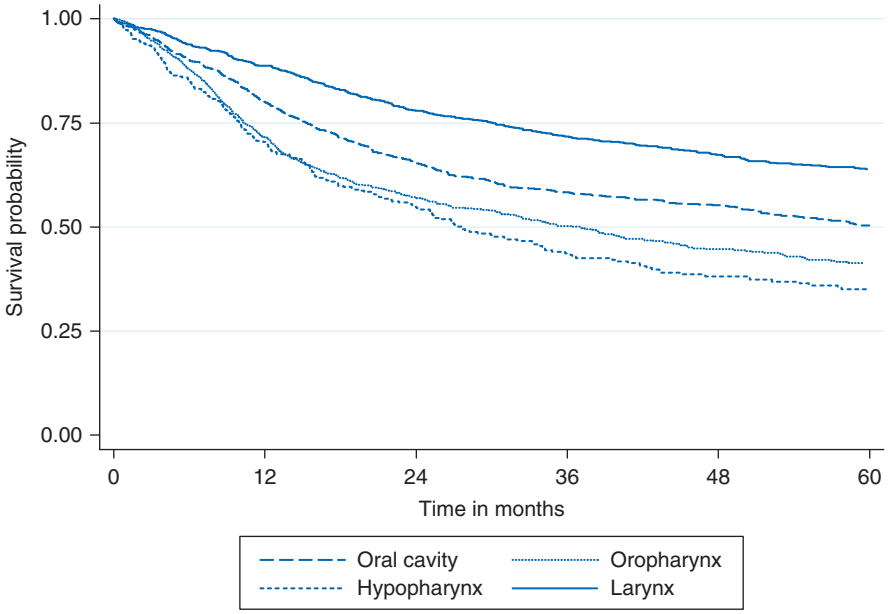

Figure 1. Kaplan–Meier unadjusted overall 5-year survival by head and neck cancer site.

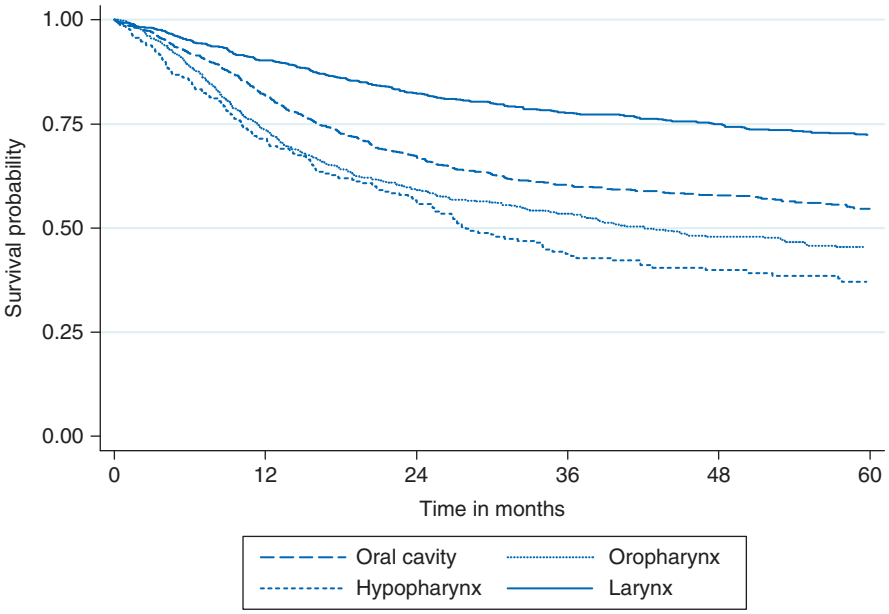

Figure 2. Kaplan–Meier unadjusted specific 5-year survival by head and neck cancer site.

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 ($P < 0.001$) 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 = 1.02, 95% CI 1.01–1.03), for oral cavity cancer (HR = 1.02, 95% CI 1.01–1.03), for oropharyngeal cancer (HR = 1.02, 95% CI 1.00–1.03) and for laryngeal cancer (HR = 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 with those having more than high school education (HR = 2.54, 95% CI 1.01–6.38).

Compared with patients with tumour stage I, patients with tumour stage IV reported a reduced OS for HNC overall (HR = 3.48, 95% CI 2.77–4.37), for oral cavity cancer (HR = 3.81, 95% CI 2.65–5.48), for oropharyngeal cancer

Table 3. Adjusted predictors of OS among 4198 head and neck cancer patients by tumour site

	Subjects[a]		Oral Cavity		Oropharynx		Hypopharynx		Larynx		OC, OP, HP NS		Total	
			n = 1404		*n* = 834		*n* = 376		*n* = 1332		*n* = 252		*n* = 4198	
	n	%	HR[b]	95% CI	HR[c]	95% CI	HR[d]	95% CI	HR[e]	95% CI	HR[d]	95% CI	HR[c]	95% CI
Demographics														
Age at diagnosis	4.198		**1.02**	**1.01–1.03**	**1.02**	**1.00–1.03**	1.01	1.00–1.02	**1.03**	**1.02–1.05**	1.02	1.00–1.04	**1.02**	**1.01–1.03**
Gender														
Men	3.218	76.9	1.00		1.00		1.00		1.00		1.00		1.00	
Women	967	23.1	0.98	0.78–1.23	1.04	0.76–1.44	0.81	0.51–1.28	0.74	0.51–1.07	0.71	0.42–1.19	1.00	0.86–1.17
Missing	13	0.3												
Ethnicity														
Caucasian	3.009	71.7	1.00		1.00		1.00		1.00		1.00		1.00	
Black	240	5.7	1.04	0.74–1.48	1.07	0.62–1.83	0.82	0.44–1.52	1.21	0.68–2.16	1.23	0.57–2–67	1.06	0.83–1.35
Asian	317	7.6	1.42	0.53–3.86	6.14	0.75–50.31	**0.56**	**0.36–0.86**	1.80	0.24–13.53	2.20	0.53–9.17	1.21	0.64–2.29
Other	565	13.5	1.08	0.84–1.40	1.44	1.04–1.99	0.82	0.55–1.23	1.10	0.74–1.63	1.02	0.63–1.67	1.11	0.95–1.31
Missing	67	1.6												
Education level														
College graduate	121	3.4	1.00		1.00		1.00		1.00		1.00		1.00	
High-technical school graduate	581	16.5	1.04	0.57–1.89	1.69	0.71–3.99	1.19	0.35–4.03	**2.54**	**1.01–6.38**	1.24	0.39–3.95	1.39	0.95–2.04
Less than high school	2.828	80.1	1.04	0.60–1.82	1.74	0.76–3.95	1.96	0.62–6.17	2.32	0.95–5.66	0.83	0.30–2.32	1.37	0.95–1.95
Missing	668	15.9												
Tumour characteristics														
Stage														
I	452	13.0	1.00		1.00		1.00		1.00		1.00		1.00	
II	537	15.5	1.45	0.96–2.19	1.19	0.55–2.55	1.03	0.06–16.78	1.23	0.81–1.87	1.74	0.67–4.53	**1.43**	**1.08–1.88**
III	573	16.5	**2.28**	**1.52–3.44**	1.88	0.93–3.81	2.46	0.32–18.76	1.29	0.84–1.97	2.15	0.78–5.94	**1.86**	**1.43–2.43**
IV	1.907	55.0	**3.81**	**2.65–5.48**	**3.10**	**1.63–5.89**	5.18	0.71–37.79	**2.46**	**1.75–3.48**	**4.19**	**1.83–9.64**	**3.48**	**2.77–4.37**
Missing	729	17.4												
Comorbidity														
No	512	12.2%	1.00		1.00		1.00		1.00		1.00		1.00	
Yes	443	10.6%	1.45	0.96–2.21	1.00	0.61–1.65	0.85	0.44–1.63	1.16	0.77–1.76	nc	nc	1.15	0.91–1.46
Missing	3.243	77.3%												
Cigarette smoking														
Smoking status														
Never smokers	400	9.7	1.00		1.00		1.00		1.00		1.00		1.00	
Former	1.015	24.7	1.05	0.68–1.63	1.66	0.88–3.10	1.00	0.49–2.06	1.12	0.65–1.92	0.80	0.41–1.57	0.98	0.77–1.25
Current	2.691	65.5	1.20	0.92–1.57	**1.83**	**1.01–3.36**	1.06	0.53–2.12	1.33	0.78–2.25	0.88	0.50–1.55	1.08	0.86–1.36
Missing	92	2.2												
Years of smoking														
Never smokers	400	16.8	1.00		1.00		1.00		1.00		1.00		1.00	
≤20	401	16.8	1.05	0.68–1.63	**2.33**	**1.15–4.72**	0.81	0.35–1.90	0.95	0.48–1.85	0.48	0.20–1.19	1.08	0.80–1.47
>20	1.579	66.3	1.20	0.92–1.57	1.72	0.94–3.18	1.06	0.53–2.10	1.14	0.64–2.01	0.91	0.52–1.59	1.07	0.85–1.34
Missing	187	7.3												
Cigarettes per day														
Never smokers	400	9.9	1.00		1.00		1.00		1.00		1.00		1.00	
≤20	2.548	63.3	1.14	0.87–1.50	**1.87**	**1.01–3.48**	0.97	0.49–1.95	1.10	0.62–1.94	0.86	0.49–1.51	1.05	0.83–1.33
>20	1.077	26.8	**1.41**	**1.03–1.92**	1.66	0.88–3.15	1.12	0.55–2.27	1.17	0.64–2.11	0.92	0.48–1.76	1.10	0.86–1.42
Missing	173	4.1												
Alcohol drinking														
Drinking status														
Never drinkers	575	14.0	1.00		1.00		1.00		1.00		1.00		1.00	
Former	1.027	24.9	0.77	0.56–1.08	1.49	0.84–2.63	1.14	0.62–2.07	1.10	0.69–1.75	0.80	0.45–1.45	1.09	0.87–1.36
Current	2.519	61.1	1.08	0.81–1.44	1.36	0.79–2.36	1.37	0.77–2.42	**1.73**	**1.16–2.58**	0.85	0.51–1.42	**1.31**	**1.07–1.61**
Missing	77	1.8												
Drinks per day														
Never drinkers	575	14.9	1.00		1.00		1.00		1.00		1.00		1.00	

Continued

Table 3. *Continued*

	Subjects[a]		Oral Cavity		Oropharynx		Hypopharynx		Larynx		OC, OP, HP NS		Total	
			n = 1404		*n* = 834		*n* = 376		*n* = 1332		*n* = 252		*n* = 4198	
	n	%	HR[b]	95% CI	HR[c]	95% CI	HR[d]	95% CI	HR[e]	95% CI	HR[d]	95% CI	HR[c]	95% CI
≤1	2.307	59.8	1.01	0.76–1.34	1.46	0.81–2.62	1.23	0.69–2.21	**1.72**	**1.12–2.63**	0.88	0.53–1.45	**1.30**	**1.05–1.62**
>1	975	25.3	1.11	0.75–1.63	1.20	0.67–2.18	1.28	0.67–2.46	**1.61**	**1.04–2.51**	0.69	0.35–1.38	**1.27**	**1.00–1.61**
Missing	341	8.1												

[a]Number of subject and percentages is referred to all HNC sites together.
[b]HR adjusted by age at diagnosis, stage, smoking status and study centre.
[c]HR adjusted by age at diagnosis, gender, stage, education level, smoking status, alcohol drinking status and study centre.
[d]HR adjusted by age at diagnosis and study centre.
[e]HR adjusted by age at diagnosis, gender, stage, education level, alcohol drinking status and study centre.
CI, confidence interval; HNC, head and neck cancer; HR, hazard ratio; HP, hypopharynx; nc, not computable; NOS, not otherwise specified; OC, oral cavity; OP, oropharynx. Text in bold indicates statistically significant risk factors.

(HR = 3.10, 95% CI 1.63–5.89) and for laryngeal cancer (HR = 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 = 1.83, 95% CI 1.01–3.36; ≤20 years of smoking, HR = 2.33, 95% CI 1.15–4.72; ≤20 cigarette per day, HR = 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 = 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 = 1.73, 95% CI 1.16–2.58; ≤1 drinks per day, HR = 1.72, 95% CI 1.12–2.63; >1 drinks per day HR = 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 category college graduates, patients with an education less than high school reported a reduced HNC-specific survival considering HNC overall (high-technical school graduate, HR = 1.48, 95% CI 1.01–2.15; less than high school, HR = 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 = 3.42, 95% CI 2.24–5.22; oropharynx, HR = 3.97, 95% CI 1.86–8.48; larynx, HR = 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 = 2.11, 95% CI 1.22–3.66; ≤1 drinks per day, HR = 2.07, 95% CI 1.17–3.69; >1 drinks per day HR = 1.92, 95% CI 1.04–3.53).

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 investigated the OS among HNC sites [2, 3, 18]. A study that investigated 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 survival rate of 62% for HNC overall: 55% for oral cavity, 53% for oropharynx, 41% for hypopharynx and 71% for larynx [18].

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 [14]. In this study, we reported an association between educational 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, 18–23]. A population-based study conducted in Italy and not included in the current pooled analysis reported an association between

Table 4. Adjusted predictors of head and neck-specific survival among 3904 head and neck cancer patients by tumour site

	Subjects[a]		Oral Cavity		Oropharynx		Hypopharynx		Larynx		OC, OP, HP NS		Total	
			n = 1257		*n* = 785		*n* = 329		*n* = 1281		*n* = 252		*n* = 3904	
	n	%	HR[b]	95% CI	HR[c]	95% CI	HR[d]	95% CI	HR[c]	95% CI	HR[e]	95% CI	HR[c]	95% CI
Demographics														
Age at diagnosis	3.904		1.01	1.00–1.02	**1.02**	**1.00–1.03**	1.00	0.99–1.02	**1.02**	**1.00–1.03**	1.01	1.00–1.03	**1.01**	**1.00–1.02**
Gender														
Men	2.985	76.7	1.00		1.00		1.00		1.00		1.00		1.00	
Women	906	23.3	1.01	0.78–1.31	1.11	0.79–1.55	0.94	0.56–1.55	0.95	0.59–1.52	0.74	0.42–1.32	1.11	0.93–1.33
Missing	13	0.3												
Ethnicity														
Caucasian	3.009	71.7	1.00		1.00		1.00		1.00		1.00		1.00	
Black	240	5.7	1.10	0.77–1.58	1.01	0.58–1.76	0.94	0.51–1.76	1.15	0.63–2.11	1.29	0.55–3.04	1.05	0.81–1.36
Asian	317	7.6	1.38	0.44–4.37	4.86	0.59–40.23	0.33	0.05–2.35	1.49	0.19–11.46	2.50	0.57–11.08	1.25	0.61–2.55
Other	565	13.5	1.12	0.85–1.48	**1.46**	**1.06–2.03**	0.81	0.52–1.27	0.91	0.58–1.41	0.91	0.53–1.59	1.07	0.89–1.27
Missing	67	1.6												
Education level														
College graduate	121	3.4	1.00		1.00		1.00		1.00		1.00		1.00	
High-technical school graduate	581	16.5	1.09	0.63–1.92	1.5	0.63–3.58	1.48	0.43–5.10	2.20	0.67–7.20	2.93	0.91–9.43	**1.48**	**1.01–2.15**
Less than high school	2.828	80.1	1.03	0.62–1.70	1.72	0.76–3.92	2.47	0.78–7.78	2.00	0.63–6.32	1.25	0.45–3.84	**1.45**	**1.02–2.06**
Missing	374	9.6												
Tumour characteristics														
Stage														
I	399	12.6	1.00		1.00		1.00		1.00		1.00		1.00	
II	468	14.7	1.33	0.81–2.17	1.54	0.64–3.69	1.48	0.09–24.15	1.40	0.71–2.75	4.15	0.92–18.72	**1.72**	**1.21–2.47**
III	526	16.6	**1.90**	**1.17–3.08**	2.08	0.91–4.72	1.58	0.20–12.47	**2.03**	**1.10–3.77**	**5.62**	**1.21–26.06**	**2.30**	**1.63–3.124**
IV	1.782	56.1	**3.42**	**2.24–5.22**	**3.97**	**1.86–8.48**	3.48	0.50–25.81	**4.58**	**2.69–7.80**	**10.43**	**2.55–42.62**	**4.73**	**3.49–6.41**
Missing	729	18.7												
Comorbidity														
No	512	12.2%	1.00		1.00		1.00		1.00		1.00		1.00	
Yes	443	10.6%	1.46	0.94–2.27	1.12	0.66–1.92	0.85	0.42–1.71	1.69	0.91–3.15	nc	nc	1.25	0.94–1.64
Missing	3.243	77.3%												
Cigarette smoking														
Smoking status														
Never smokers	331	8.7	1.00		1.00		1.00		1.00		1.00		1.00	
Former	943	24.7	0.87	0.59–1.27	1.60	0.83–3.08	1.10	0.43–2.83	1.02	0.50–2.08	0.89	0.43–1.86	0.92	0.70–1.21
Current	2.538	66.6	1.08	0.78–1.48	1.52	0.81–2.86	1.18	0.47–2.94	0.90	0.45–1.80	0.89	0.47–1.66	0.93	0.72–1.21
Missing	92	2.4												
Years of smoking														
Never smokers	331	8.9	1.00		1.00		1.00		1.00		1.00		1.00	
≤20	366	9.8	1.07	0.65–1.75	1.73	0.83–3.60	0.87	0.30–2.60	0.73	0.29–1.84	0.53	0.20–1.41	0.88	0.63–1.24
>20	3.024	81.3	1.06	0.77–1.47	1.43	0.76–2.69	1.19	0.48–2.95	0.97	0.46–2.03	0.93	0.50–1.72	0.92	0.71–1.19
Missing	183	4.7												
Cigarettes per day														
Never smokers	331	67.6	1.00		1.00		1.00		1.00		1.00		1.00	
≤20	2.416	27.6	1.01	0.73–1.41	1.50	0.79–2.83	1.05	0.42–2.62	0.94	0.45–1.99	0.83	0.44–1.56	0.90	0.69–1.16
>20	987	4.8	1.28	0.89–1.84	1.32	0.68–2.56	1.37	0.54–3.49	0.99	0.46–2.14	1.10	0.54–2.23	0.97	0.73–1.28
Missing	170	4.4												
Alcohol drinking														
Drinking status														
Never drinkers	500	29.8	1.00		1.00		1.00		1.00		1.00		1.00	
Former	1.014	67.9	0.75	0.50–1.10	1.52	0.85–2.74	0.93	0.49–1.74	1.24	0.68–2.27	0.89	0.47–1.70	1.07	0.83–1.38
Current	2.313	2.3	1.01	0.72–1.44	1.41	0.79–2.49	1.10	0.60–2.01	**2.11**	**1.22–3.66**	0.88	0.50–1.54	**1.31**	**1.04–1.66**
Missing	77	2.0												
Drinks per day														
Never drinkers	500	61.4	1.00		1.00		1.00		1.00		1.00		1.00	

Continued

Table 4. *Continued*

	Subjects[a]		Oral Cavity		Oropharynx		Hypopharynx		Larynx		OC, OP, HP NS		Total	
			n = 1257		*n* = 785		*n* = 329		*n* = 1281		*n* = 252		*n* = 3904	
	n	%	HR[b]	95% CI	HR[c]	95% CI	HR[d]	95% CI	HR[c]	95% CI	HR[e]	95% CI	HR[c]	95% CI
≤1	2.091	28.6	0.97	0.69–1.37	1.53	0.84–2.78	0.97	0.52–1.80	**2.07**	**1.17–3.69**	0.93	0.53–1.62	**1.32**	**1.03–1.69**
>1	975	9.9	0.97	0.62–1.52	1.19	0.64–2.24	1.13	0.57–2.21	**1.92**	**1.04–3.53**	0.69	0.32–1.50	1.27	0.97–1.67
Missing	338	8.7												

[a]Number of subject and percentages is referred to all HNC sites together.
[b]HR adjusted by stage, smoking status and study centre.
[c]HR adjusted by gender, stage, smoking status, alcohol drinking status and study centre.
[d]HR adjusted by study centre.
[e]HR adjusted by stage.
nc, not computable; CI, confidence interval; HNC, head and neck cancer; HR, hazard ratio; HP, hypopharynx; nc, not computable; NOS, not otherwise specified; OC, oral cavity; OP, oropharynx. Text in bold indicates statistically significant risk factors.

smoking and survival from laryngeal cancer, while no effect of alcohol consumption was found [20]. The same relationship was later explored by larynx subsites, reporting cigarette smoking as an independent prognostic factor for the cancer of the endolarynx 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 patients 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 hypopharyngeal cancer [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 comorbidities when investigating the cancer-specific survival, and the lack of information on HPV status when investigating the survival 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 individual 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 subsites and to adjust for multiple factors when estimating the prognostic factors for specific HNC subsites.

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 educational level also had an unfavourable prognosis. Additional studies including a large sample of patients that allow the adjustment for the main confounders, including comorbidities, and the lifestyle habits after the diagnosis might define and will highlight the differences of HNC subsites in terms of lifestyle related prognostic factors.

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Disclosure

The authors have declared no conflicts of interest.

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