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# CLINICAL FEATURES AND PROGNOSTIC FACTORS IN PATIENTS WITH HEAD AND NECK CANCER: RESULTS FROM A MULTICENTRIC STUDY

Emanuele Leoncini <sup>a,j</sup>, Vladimir Vukovic <sup>a</sup>, Gabriella Cadoni <sup>b</sup>, Roberta Pastorino <sup>a</sup>, Dario Arzani <sup>a</sup>, Cristina Bosetti <sup>c</sup>, Cristina Canova <sup>d</sup>, Werner Garavello <sup>e</sup>, Carlo La Vecchia <sup>f</sup>, Milena Maule <sup>g</sup>, Livia Petrelli <sup>b</sup>, Enrico Pira <sup>h</sup>, Jerry Polesel <sup>i</sup>, Lorenzo Richiardi <sup>g</sup>, Diego Serraino <sup>i</sup>, Lorenzo Simonato <sup>d</sup>, Walter Ricciardi <sup>a</sup>, Stefania Boccia <sup>a,j</sup>

<sup>a</sup> Section of Hygiene, Institute of Public Health, Università Cattolica del Sacro Cuore, L.go F. Vito, 1, Rome 00168, Italy

<sup>b</sup> Institute of Otorhinolaryngology, Università Cattolica del Sacro Cuore, L.go F. Vito, 1, Rome 00168, Italy

<sup>c</sup> IRCCS, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Via La Masa 19, 20156 Milan, Italy

<sup>d</sup> Laboratory of Public Health and Population Studies, Department of Molecular Medicine, Via Loredan 18, 35131 Padua, Italy

<sup>e</sup> Clinica Otorinolaringoiatrica, Department of Surgery and Translational Medicine, Università degli Studi di Milano Bicocca, Via Cadore 48, 20053 Milan, Italy

<sup>f</sup> Department of Clinical Sciences and Community Health, University of Milan, Via Venezian 1, 20133 Milan, Italy

<sup>g</sup> Department of Medical Sciences, University of Turin, Turin, Corso Dogliotti 14, 10126 Turin, Italy

<sup>h</sup> Department of Public Health and Paediatrics, University of Turin, Via Zuretti n. 29, 10126 Turin, Italy

<sup>i</sup> SOC Epidemiologia e Biostatistica, IRCCS Centro di Riferimento Oncologico, Via F. Gallini 2, 33081 Aviano, Italy

<sup>j</sup> IRCCS San Raffaele Pisana, Via della Pisana, 235, 00163 Rome, Italy

## ABSTRACT

**Background:** The purpose of this study is to evaluate whether demographics, lifestyle habits, clinical data and alcohol dehydrogenase polymorphisms rs1229984 and rs1573496 associated with first primary head and neck (HNC) are associated with overall survival, recurrence, and second primary cancer (SPC).

**Methods:** We conducted a follow-up study in five centres including 801 cases. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for overall survival, recurrence and SPC.

**Results:** Five-years overall survival was 62% for HNC cases, 55% for oral cavity, 53% for oropharynx, 41% for hypopharynx, and 71% for larynx. Predictors of survival were older ages (HR = 1.18 for 5 years increase; CI: 1.07–1.30), higher tumour stage (HR = 4.16; CI: 2.49–6.96), and high alcohol consumption (HR = 3.93; CI: 1.79–8.63). A combined therapy (HR = 3.29; CI: 1.18–9.13) was associated with a worst prognosis for oral cavity cancer. The only predictor was higher tumour stage (HR = 2.25; CI: 1.26–4.03) for recurrence, and duration of smoking (HR = 1.91; CI: 1.00–3.68) for SPC. ADH1B rs1229984 polymorphism HRs for HNC and oesophageal cancer death and for alcohol related cancer death were 0.67 (95% CI: 0.42–1.08), and 0.64 (95% CI: 0.40–1.03), respectively.

**Conclusions:** The survival expectation differs among HNC sites. Increasing age and stage, and high alcohol consumption were unfavourable predictors of HNC survival overall. Duration of tobacco consumption before the first primary tumour was a risk factor for SPC.

**Keywords:** Head and neck cancer, Survival, Recurrence, Second primary

## 1. Introduction

Cancers of the head and neck (HNC) are the sixth most common cancer worldwide, with more than half a million new cases and over 450,000 deaths in 2012 [1]. These malignancies include cancers of the oral cavity, oropharynx, hypopharynx, and larynx, and 90% are squamous cell carcinomas [2]. Tobacco smoking and alcohol consumption are the predominant risk factors for HNC [3,4], with human papillomavirus (HPV) infection (for oropharynx), diet, physical activity, and nutrition also playing an important role [5–7]. A family history of HNCs in first degree relatives increases the risk of HNCs [8,9], indicating that genetic factors might be involved in the pathogenesis of HNC.

Polymorphisms in genes encoding for metabolism of alcohol to acetaldehyde [alcohol dehydrogenase gene family (ADH)] and from acetaldehyde to acetate [aldehyde dehydrogenase 2 (ALDH2)], and CYP2E1 polymorphisms, are suspect in HNC and other alcohol-related cancer aetiology [10–19]. In particular, a significant protective effect of two single nucleotide polymorphisms (SNPs) towards upper aero-digestive tract cancer (UADT) was reported for two alcohol dehydrogenase genes: ADH1B (rs1229984) and ADH7 (rs1573496) [20].

In Europe, the 5-year survival rate varies considerably according to anatomic site, 63.1% for cancer of the larynx, 48.5% for oral cavity, 39.8% for oropharynx and 25.5% for hypopharynx cancer [21]. About 40–60% of HNC patients develop recurrences, and around 20% of HNCs develop second primary cancer (SPC), both being associated with poorer survival [22].

Despite various therapeutic interventions, including surgery, radiotherapy, and chemotherapy, the 5-year survival rate for this disease has improved only marginally during the past two decades. For patients with disease confined to the head and neck, there are two major and distinct patterns of treatment failures after definitive therapy: recurrence of primary disease (local, regional or distant) and development of SPC [23,24]. The 5-year survival rate after SPC diagnosis is about 8% if the malignancy is outside the head and neck area, and increased to 30% if the SPC is an HNC [25]. So far, few studies examined the prognostic significance of gene polymorphisms in alcohol metabolism and oxidative stress-related genes in patients with HNC, and they reported evidence of an association of specific polymorphisms with survival (CYP2E1, ADH3) or higher recurrence (CYP1A2) [14,15,26]. The purpose of our study is to evaluate whether two specific alcohol dehydrogenase genes [ADH1B (rs1229984) and ADH7 (rs1573496)], and established demographics and lifestyle-related risk factors for HNC, influence overall survival, recurrence, and development of SPC in HNC patients. To explore these issues we conducted a multicentre follow-up study in Italy, including five Italian centres totalling 801 HNC cases.

## **2. Materials and methods**

Subjects with histologically confirmed primary squamous cell carcinoma of the head and neck were included. Participants were drawn from five Italian centres located in different regions, that are members of the International Head and Neck Cancer Epidemiology (INHANCE) Consortium [27]. The centres are located in: Aviano (Friuli Venezia Giulia), Milan (Lombardy), Padua (Veneto), Rome (Latium), and Turin (Piedmont). The Aviano, Padua and Turin centre are the Italian centres of the European ARCAGE case–control study on HNC cancer [28].

The study was approved by the local Ethical Committees at each participating centre. HNC tumours were classified into anatomic site according to the following ICD-O-2 categories: oral cavity (codes 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 (codes 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 (codes C12.9, C13.0–C13.2, C13.8, and C13.9), oral cavity or pharynx overlapping or not otherwise specified (codes C02.8, C02.9, C05.8, C05.9, C14.0, C14.2, and C14.8), larynx (codes C32.0–C32.3 and C32.8–C32.9). The tumours were staged according tumour, node, metastasis (TNM) classification [29].

The recruitment was conducted from 2002 to 2005 in Aviano, Padua, and Turin, while from 2001 to 2009 in Milan and from 2002 to 2012 in Rome. The participation rates ranged across centres from 88% in Turin to 98% in Rome.

### *2.1 Data collection*

Patients were interviewed face-to-face in all centres by trained interviewers or medical doctors, on demographics, alcohol and tobacco consumption, and other relevant lifestyle factors. Health behaviours questions focused on the time period ending 1 year prior to diagnosis.

Participants were also followed from the date of diagnosis to the date of death, end of follow-up at June 30, 2013, or loss to 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. Cancer recurrence and SPC were collected from medical records and cancer registries. Data on tumour pathology and treatment were obtained from pathology records. Only the centre of Milan did not have active follow-up of cancer cases and medical records were not used as source of information for recurrence and SPC.

Standard data collection forms were used by all the centres to collect the aforementioned information. Data from individual centres were received from the coordinating centre at the Università Cattolica del Sacro Cuore in Rome. All data were checked for internal consistency and clarifications were requested from the original investigators when needed.

## *2.2. Genotyping*

The genotyping of the European ARCAGE and Rome studies was conducted using Illumina Sentrix HumanHap300 BeadChip at the Centre d'Etude du Polymorphisme Humain, as described previously [30]. Quality control for each genotyping was performed in each experiment, and 10% of the total samples were randomly selected and retested with 100% concordance.

The genotyping of the Milan study of the two SNPs rs1229984 (ADH1B) and rs1573496 (ADH7) was performed by Applied Biosystems TaqMan Drug Metabolism Genotyping Assay at the coordinating centre. DNA was extracted from peripheral blood lymphocytes.

## *2.3. Outcomes definition*

The primary endpoint was overall survival (OS), measured as the time from the date of initial diagnosis of index primary tumours to the date of death from any cause. All observations were censored at loss to follow-up and at the end of the study period.

Recurrence was defined as the local, regional or distant return of cancer after that the patient was defined as disease free.

By definition, a second primary tumour of the same histologic type as the first had to be separated from it by more than 2 cm of normal epithelium or had to occur at least 3 years after diagnosis of the first primary tumour. Any new tumour of a different histologic type was characterized as a second primary tumour without the requirement of a separation of more than 2 cm [31].

We defined alcohol-related cancers as those for which the International Agency for Research on Cancer (IARC) has concluded there is sufficient evidence of carcinogenicity in human beings in relation to active alcohol drinking [32]: oral cavity, pharynx, larynx, oesophagus, and liver, and, additionally breast cancer and colorectal cancer.

## *2.4. Statistical analysis*

We used the Kaplan–Meier method to calculate the cumulative proportion surviving and to plot the survival curves. We used the multivariable Cox's proportional hazards model to determine independent predictors of OS, recurrence and SPC. We formally tested the Cox proportional hazards assumption for each covariate using Schoenfeld residuals [33]. Hazard ratios (HR) for all-cause mortality were adjusted for age at diagnosis, gender, tumour stage, and comorbidity. In the multivariable analysis, we also excluded all cases from Milan centre because information on tumour stage was not available.

Models to predict SPC were adjusted for age at diagnosis and tumour stage. The association between SNPs and various outcomes was explored using univariate analysis.

With respect to smoking, patients were classified as never, former, or current smokers. Cumulative tobacco consumption was calculated as intensity of smoking (never smokers,  $\leq 20$  cigarettes/day,

>20 cigarettes/day), and smoking duration in years (never smokers,  $\leq 20$ , 21–40, >40). With respect to alcohol drinking,

subjects were classified as never drinkers, former and current, and according to alcohol consumption (none or <1 drink equivalent/ day, 1–2 drinks/day, >2 drinks/day). The standard definition for one drink equivalent was 14 g ethanol, which approximately corresponds to 150 mL wine, 330 mL beer, and 36 mL spirits [32].

The genotypes of rs1229984 and rs1573496 were dichotomized according to presence versus absence of the minor allele.

Analyses were performed for overall HNC and for individual subsites (oral cavity, oropharynx, hypopharynx, larynx) where possible. Statistical analyses were performed using Stata software, version 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

### 3. Results

A total of 801 subjects were included in the study from the five Italian centres (Table 1). Disease location was oral cavity in 191 (23.8%) patients, oropharynx in 139 (17.4%), hypopharynx in 43 (5.4%), and larynx in 398 (49.7%). For the remaining 30 patients (3.7%), the disease location was oral cavity or pharynx not otherwise specified.

#### 3.1. Overall survival

There were 164 (20.5%) women and 637 (79.5%) men, with a median age at diagnosis of 62 (range: 27–88) years. Median follow-up time since cancer diagnosis was 59 months (interquartile range: 20–92). During the follow-up, 358 of 801 cases (44.7%) had died, of which 227 (63.4%) died from HNC and oesophageal cancer and 49 (13.7%) from other cancers. Five-years overall survival for all HNC sites combined was 62% (IQ range 59–66%): oral cavity 55% (IQR 47–62%), oropharynx 53% (IQR 44–61%), hypopharynx 41% (IQR 26–56%), and larynx 71% (IQR 66–76%). Median survival time in months was higher for laryngeal cancer than for the other tumour sites [63 months versus 53 (oral cavity  $p = 0.006$ ), 49 (oropharynx  $p = 0.001$ ), 50 (hypopharynx  $p = 0.125$ )] (Fig. 1). Table 2 presents the distribution for selected covariates and the HR for all-cause mortality adjusted by age at diagnosis, gender, tumour stage, and comorbidity by HNC sites and combined. A reduced survival was associated with increasing age, with an HR of 1.18 (95% CI: 1.07–1.30) for all HNC sites for every 5-years increase. Results were still significant when stratified according to HNC sites, except for oropharynx.

A tumour stage IV was a negative prognostic factor for cancer of oral cavity (HR = 3.34; 95% CI: 1.30–8.59) and larynx (HR = 4.19; 95% CI: 1.93–9.10). For all HNC combined, the HR was 1.94 (95% CI: 1.10–3.43) for stage II patients, 2.89 (95% CI: 1.62–5.14) for stage III patients, and 4.16 (95% CI: 2.49–6.96) for stage IV patients.

A combined therapy including radiotherapy plus surgical treatment and chemotherapy was a negative prognostic factor for cancer of oral cavity (HR = 3.29; 95% CI: 1.18–9.13).

In univariate analysis only, cigarette smoking was a negative prognostic factor for those current smokers before diagnosis of oral cavity cancer (HR = 1.78; 95% CI: 1.05–3.03) compared to never smokers. The death rate among subjects who had smoked more than 40 years, was significantly higher in patients with oral cavity (HR = 2.26; 95% CI: 1.25–4.07) and oropharynx tumour (HR = 2.38; 95% CI: 1.11–5.11), as well as in patients with HNC in general (HR = 1.54; 95% CI: 1.09–2.17). However, these patterns did not persist after adjustment for significant prognostic factors.

Excessive alcohol use was associated with an increased hazard of all-cause deaths when we considered all HNC sites (1–2 drinks per day, HR = 2.83; 95% CI: 1.30–6.16; >2 drinks per day, HR = 3.93; 95% CI: 1.79–8.63).

### 3.2. Cancer recurrence

Among the 771 HNC patients included (30 patients with cancer of the oral cavity or pharynx not otherwise specified were excluded), disease recurrence was unknown for 132 subjects (17.1%) and additional 53 (6.8%) subjects did not report the date of recurrence, thus leaving 586 (76.0%) eligible patients with complete information on recurrence. A total of 149 (25.4%) patients with recurrence were included in the analysis. Demographic, clinical, and lifestyle characteristics and the association with recurrence are reported in Table 3. The risk of recurrence was associated with the highest stage for HNC (HR = 2.25, 95% CI 1.26–4.03). No significant association was reported for alcohol drinking and smoking habits (Table 3).

### 3.3. Second primary cancer

Information on SPC was available for 613 (79.5%) patients. Among them, 117 (19%) developed a SPC during follow-up period. The most frequent SPC sites were HNC (32.7%) and lung (27.7%) (data not shown). The risk for developing SPC increased with increasing years of smoking. Taking never smoking as the reference, the HR for developing SPC was 1.91 (95% CI: 1.00–3.68) in patients who smoked more than 40 years. By restricting the analysis to second primary alcohol related and smoke related cancers, results did not change (data not shown).

### 3.4. ADH1B (*rs1229984*) and ADH7 (*rs1573496*)

Genotyping data on ADH1B and ADH7 SNPs was available for 702 (91%) subjects, and their association with prognosis is reported in Table 4. In unadjusted analyses, the HRs for ADH1B *rs1229984*, though not statistically significant, were suggestive of differences in risk for HNC and oesophageal cancer death (HR = 0.67; 95% CI: 0.42–1.08), and for all alcohol-related cancer deaths (HR = 0.64; 95% CI: 0.40–1.03). We did not find a significant association between the selected SNPs and recurrence or SPC.

## 4. Discussion

We evaluated the prognostic significance of demographics, alcohol and tobacco, clinical features and selected polymorphisms of genes ADH1B and ADH7 on overall survival, recurrence and occurrence of SPC in a large cohort of HNC patients.

Our results show that 5-year overall survival was 62%, similar to that reported in a previous study [34]. Survival differed largely among HNC sites: as expected from previous studies, larynx cancers had the best and hypopharynx cancers had the worst prognosis [34].

Predictors of overall survival of HNC were older ages, higher tumour stage, and high alcohol consumption. Additionally, considering the specific HNC sites, a combined therapy including radiotherapy plus surgical treatment and chemotherapy, was a negative prognostic factor for oral cavity cancer.

Several epidemiologic studies in different head and neck sites have examined the association between alcohol consumption prediagnosis and survival/increased risk of death, sometimes in a dose-dependent fashion, with conflicting results [35–38]. A multicentric population-based case–control study of laryngeal and hypopharyngeal cancer carried out in six European regions, reported that alcohol drinking affects the survival, albeit to a limited extent [36]. However, more recent studies that have examined the effect of alcohol drinking on survival reported opposite results [37,38].

Evidence is accruing that smoking may also be causally related with increased all-cause mortality. One study reported that the effect of smoking was evident only among the chemoradiotherapy or radiotherapy group [37]; another, found that smoking status was the strongest predictor of survival, in both current and former smokers [38]; a third large population-based study from Ireland, involving 5652 patients with HNC, reported significantly increased cancer-related death rate for current smokers with oral cavity, pharyngeal, and laryngeal cancers, and the association was stronger in surgically treated patients [39]. Moreover, the association between cigarette smoking and survival has been demonstrated also in colon [40], pancreatic cancer [41], renal cell carcinoma [42], oropharyngeal [43], and nasopharyngeal carcinoma [44] highlighting a possible enduring effects of smoking, even after stopping.

In our study, smoking status at diagnosis is not an independent prognostic factor of overall survival among patients with HNC. One possible explanation for this is that current smokers will have been recorded as ex-smokers, which would mean that the true effect of smoking at diagnosis on mortality has been underestimated.

In our study, cancer recurrence was associated with higher tumour stage of the disease and duration of cigarette smoke is a predictor of SPC. An extensive literature shows that the most frequent SPC sites after first HNC is HNC, lung and oesophagus as these are tobacco and alcohol related tumours [45–49], however there are conflicting results about the factors associated with the development of SPCs. Slaughter et al. [50] proposed the theory of field cancerization, where carcinogenic effects from tobacco and alcohol may act on multiple places of the aerodigestive tract mucosa, triggering the development of multiple lesions. Previous reports suggested that additional prognostic factors for SPC among HNC patients are older age, hypopharyngeal index tumour site, and heavy alcohol consumption among Asians [47].

We investigated the associations between ADH1B rs1229984 and ADH7 rs1573496 polymorphisms with overall survival, recurrence, and SPC. Recent studies showed that SPC can share some genetic markers with the index tumours and that they can derive from the same genetically altered mucosal field as the primary tumour [51]. ADH1B, with ADH1A and AD1C, accounts for most of the ethanol oxidizing capacity in the liver, whereas the enzyme coded by ADH7 is active as a retinol dehydrogenase and its expression is much more abundant in stomach than liver. ADH1B rs1229984 and ADH7 rs1573496 variants were identified to be protective against aerodigestive cancer in European and Latin American populations [20]. A genome-wide association study conducted in two European case–control studies on upper aerodigestive tract cancer and further studies in a Chinese and Japanese population supported this association [30,52,53].

In our study, ADH1B rs1229984 polymorphism were not consistently related with HNC and oesophageal cancer and alcohol-related cancer deaths. Moreover no influence on recurrence or SPC was observed. rs1229984 (ADH1B) G/T heterozygotes and T/T homozygotes are known to metabolize ethanol up to 40 times quicker than the common rs1229984 (ADH1B) G/G homozygote, providing support that quick eradication of ethanol, and therefore lower local exposure, may be protective also on the prognosis. The only study addressing such associations, however, did not report a protective effect of the aforementioned SNPs [14]. In interpreting our results some limitations should be acknowledged. Firstly, in the analysis of recurrence and SPC we were unable to stratify according to HNC site due to reduced power.

Secondly, we did not have information on HPV status which is a well-known prognostic factor for oropharyngeal cancer [54]. Thirdly, information on tobacco smoking and on alcohol drinking after treatment of the index tumour, that might additionally influence SPC occurrence, was not collected. Results show that advanced age, tumour stage, and alcohol consumption were predictors of HNC survival. Predictors of recurrence was HNC stage, while SPC risk was associated with smoking duration. Lastly, the ADH1B rs1229984 polymorphism could be associated with a better prognosis.

Additional studies including a larger set of HNC patients might provide insights into the prognostic factors for recurrence and SPC by cancer sites. Further SNPs of the ADH gene should be genotyped and analysed to completely capture the influence this family gene in the prognosis of HNC.

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### **Conflict of interest**

The authors have declared no conflicts of interest.

### **Authorship contribution**

Emanuele Leoncini: data quality control, statistical analysis, interpretation of data, manuscript preparation. Vladimir Vukovic, Werner Garavello, Milena Maule, Livia Petrelli: data acquisition, manuscript review. Gabriella Cadoni, Dario Arzani, Cristina Bosetti, Cristina Canova, Carlo La Vecchia, Jerry Polesel, Lorenzo Richiardi, Diego Serraino, Lorenzo Simonato: study design, interpretation of data, manuscript review. Roberta Pastorino: statistical analysis, manuscript preparation, manuscript review. Enrico Pira: data acquisition, interpretation of data, manuscript review. Walter Ricciardi: study concepts, study design, manuscript review. Stefania Boccia: study concepts, study design, manuscript preparation, manuscript review.

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**Table 1**

Characteristics of 801 cases of head and neck cancer in 5 Italian centres according to tumour site

Study location	Recruitment period	Case source	Participation rate, %	Site of cancer											
				Oral cavity (OC)		Oropharynx (OP)		Hypopharynx (HP)		Larynx		OC, OP, HP, NOS		Total	
				n	%	n	%	n	%	n	%	n	%	n	%
Aviano	2002-2005	Hospital	82	46	37.4	34	27.6	9	7.3	32	26.0	2	1.6	123	15.4
Milano	2001-2009	Hospital	>95	31	19.3	9	5.6	8	5.0	108	67.1	5	3.1	161	20.1
Padova	2002-2005	Hospital	82	25	21.4	26	22.2	14	12.0	51	43.6	1	0.9	117	14.6
Rome	2002-2012	Hospital	98	39	13.6	48	16.7	5	1.7	176	61.3	19	6.6	287	35.8
Turin	2003-2005	Hospital	82	50	44.2	22	19.5	7	6.2	31	27.4	3	2.7	113	14.1
<b>Total</b>				<b>191</b>	<b>23.8</b>	<b>139</b>	<b>17.4</b>	<b>43</b>	<b>5.4</b>	<b>398</b>	<b>49.7</b>	<b>30</b>	<b>3.7</b>	<b>801</b>	<b>100.0</b>

NOS: not otherwise specified

**Table 2**

Predictors of overall survival among 801 head and neck cancer (HNC) cases by tumour site by multivariable analysis

	Death from all causes													
	Subjects		Oral cavity (TOT/deaths: 191/101)				Oropharynx (TOT/deaths: 139/76)				Larynx (TOT/deaths: 39/14)		Total (TOT/deaths: 801/358)	
	n	%	HR (95% CI)	HR adj (95% CI)	HR (95% CI)	HR adj (95% CI)	HR (95% CI)	HR adj (95% CI)	HR (95% CI)	HR adj (95% CI)	HR (95% CI)	HR adj (95% CI)		
<b>Demographics</b>														
Age at diagnosis			<b>1.18 (1.06-1.31)</b>	<b>1.23 (1.03-1.47)</b>	<b>1.20 (1.04-1.38)</b>	1.14 (0.91-1.43)	<b>1.38 (1.24-1.54)</b>	<b>1.29 (1.06-1.56)</b>	<b>1.19 (1.12-1.27)</b>	<b>1.18 (1.07-1.30)</b>				
<55	196	24.5												
55-59	120	15.0												
60-64	140	17.5												
65-69	133	16.6												
70-74	118	14.8												
>75	92	11.5												
Gender														
Women	164	20.5	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00		
Men	637	79.5	1.20 (0.70-1.83)	1.59 (0.80-3.16)	0.75 (0.45-1.23)	0.97 (0.43-2.10)	0.86 (0.53-1.39)	2.16 (0.76-6.17)	0.36 (0.07-1.10)	1.42 (0.93-2.16)				
Education level														
High school or more	253	31.8	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00		
Less than high school	543	68.2	0.94 (0.62-1.43)	0.75 (0.37-1.55)	1.10 (0.69-1.78)	1.16 (0.55-2.43)	1.32 (0.90-1.94)	1.02 (0.55-1.89)	1.10 (0.88-1.39)	1.04 (0.73-1.48)				
<b>Tumour/treatment characteristics</b>														
Stage (#)														
I	124	25.6	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00		
II	107	22.1	1.31 (0.56-3.06)	1.40 (0.49-4.01)	0.32 (0.08-1.33)	1.01 (0.17-6.09)	1.86 (0.96-3.61)	2.02 (0.91-4.45)	1.47 (0.92-2.36)	<b>1.96 (1.10-3.43)</b>				
III	91	18.8	2.44 (0.66-9.01)	2.28 (0.68-7.65)	1.83 (0.68-4.92)	<b>4.55 (1.00-20.09)</b>	1.41 (0.65-3.09)	1.50 (0.55-4.12)	<b>2.16 (1.36-3.43)</b>	<b>2.86 (1.60-5.14)</b>				
IV	163	33.6	<b>2.90 (1.37-6.24)</b>	<b>3.34 (1.30-8.59)</b>	1.84 (0.71-4.79)	3.35 (0.75-15.03)	<b>3.14 (1.65-5.89)</b>	<b>4.19 (1.93-9.10)</b>	<b>3.24 (2.17-4.85)</b>	<b>4.16 (2.49-6.96)</b>				
Treatment (§)														
Surgical	208	53.1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00		
Surgical and radiation	104	26.5	1.48 (0.76-2.88)	1.58 (0.61-4.05)	0.53 (0.24-1.18)	0.86 (0.20-2.38)	1.25 (0.62-2.55)	1.04 (0.32-3.31)	1.32 (0.89-1.95)	1.32 (0.74-2.36)				
Surgical, radiation, chemotherapy	80	20.4	<b>2.90 (1.48-5.90)</b>	<b>2.89 (1.18-8.11)</b>	0.64 (0.28-1.46)	0.34 (0.09-1.28)	2.03 (0.87-4.74)	1.74 (0.53-5.75)	1.84 (1.21-2.78)	1.57 (0.85-2.81)				
Comorbidity (#)														
No	159	34.6	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00		
Yes	301	65.4	1.13 (0.70-1.82)	1.42 (0.64-3.13)	0.91 (0.52-1.62)	1.25 (0.52-3.01)	0.99 (0.66-1.50)	1.08 (0.54-2.13)	0.98 (0.76-1.27)	1.08 (0.73-1.59)				
<b>Cigarette smoking</b>														
Smoking status														
Never	117	14.7	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00		
Former	275	34.5	1.32 (0.74-2.33)	1.02 (0.37-2.81)	2.05 (0.98-4.29)	1.00 (0.35-2.92)	0.79 (0.44-1.40)	1.52 (0.31-7.32)	1.15 (0.82-1.62)	0.96 (0.52-1.78)				
Current	404	50.8	<b>1.78 (1.03-3.07)</b>	1.77 (0.65-4.84)	1.62 (0.78-3.39)	1.36 (0.43-3.64)	0.85 (0.46-1.49)	2.03 (0.46-10.27)	1.30 (0.84-1.92)	1.47 (0.79-2.73)				
Years of smoking														
Never smokers	117	15.1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00		
<20	76	9.8	0.87 (0.36-2.07)	0.86 (0.13-3.17)	1.66 (0.56-4.96)	1.17 (0.25-5.34)	0.71 (0.33-1.51)	1.03 (0.16-6.46)	0.91 (0.57-1.48)	0.77 (0.34-1.75)				
21-40	362	46.1	1.40 (0.81-2.40)	1.31 (0.48-3.56)	1.51 (0.72-3.16)	0.76 (0.26-2.21)	0.82 (0.35-1.12)	1.36 (0.27-6.77)	1.96 (0.76-4.91)	0.98 (0.53-1.82)				
>40	340	31.0	<b>2.26 (1.25-4.07)</b>	2.05 (0.65-6.48)	<b>2.38 (1.11-5.11)</b>	1.78 (0.58-5.40)	1.08 (0.61-1.90)	2.12 (0.41-10.31)	<b>1.54 (1.00-2.37)</b>	1.74 (0.92-3.30)				
Cigarettes per day														
Never smokers	117	14.7	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00		
<20	436	54.9	1.54 (0.92-2.59)	1.31 (0.51-3.37)	1.83 (0.89-3.76)	1.19 (0.43-3.26)	0.80 (0.46-1.39)	1.59 (0.33-7.67)	1.24 (0.90-1.72)	1.19 (0.65-2.15)				
>20	241	30.4	1.57 (0.82-2.99)	1.43 (0.43-4.74)	1.72 (0.79-3.76)	0.92 (0.29-2.94)	0.86 (0.48-1.54)	1.92 (0.37-10.02)	1.19 (0.84-1.70)	1.12 (0.58-2.17)				
<b>Alcohol drinking</b>														
Drinking status														
Never	100	12.5	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00		
Former	77	9.6	1.20 (0.50-2.88)	0.86 (0.24-3.07)	1.46 (0.61-3.49)	1.76 (0.44-7.06)	1.00 (0.44-2.25)	0.18 (0.03-0.92)	1.37 (0.87-2.16)	0.90 (0.46-1.77)				
Current	622	77.8	1.13 (0.59-2.18)	0.76 (0.28-2.05)	1.17 (0.56-2.40)	1.18 (0.36-3.91)	1.35 (0.77-2.35)	0.73 (0.27-1.97)	1.32 (0.93-1.89)	1.11 (0.64-1.90)				
Drinks per day														
Never drinkers or <1	105	14.9	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00		
1-2	247	30.8	1.78 (0.98-3.28)	2.13 (0.60-7.51)	1.94 (0.85-4.44)	nc	1.33 (0.73-2.41)	1.09 (0.69-1.72)	1.44 (0.99-2.08)	<b>2.00 (1.30-3.14)</b>				
>2	35	4.4	1.60 (0.68-3.81)	1.54 (0.41-5.71)	1.60 (0.75-3.40)	nc	1.45 (0.81-2.60)	4.19 (0.93-18.84)	<b>1.57 (1.11-2.24)</b>	<b>3.89 (1.79-8.63)</b>				

Text in bold indicates statistically significant risk factors.

HR: hazard ratio; CI: confidence interval; nc: not computable; TOT: total.

HR adj: HR adjusted by age, gender, stage, comorbidity. In the multivariable analysis, cases from Milan centre excluded because information on tumour stage was not available.

(#) More than 5% of the data were missing.

(§) The three most common types of cancer treatment were reported. 10% (n = 83) of the information is missing

**Table 3**

Predictors of recurrence and second primary cancer among head and neck cancer cases from multivariable analyses

	Recurrence (n=149) HR adj (95% CI) <sup>a</sup>	Second primary cancer (n=117) HR adj (95% CI) <sup>b</sup>
<b>Demographics</b>		
Age at diagnosis	0.95 (0.83-1.10)	1.08 (0.97-1.21)
<55		
55-59		
60-64		
65-69		
70-74		
≥75		
Gender		
Women	1.00	1.00
Men	1.07 (0.63-1.84)	0.88 (0.56-1.39)
Education level		
High school or more	1.00	1.00
Less than high school	0.92 (0.57-1.49)	1.43 (0.92-2.23)
<b>Tumour/treatment characteristics</b>		
Subsite		
Oral cavity	1.00	1.00
Oropharynx	0.58 (0.31-1.08)	1.43 (0.77-2.67)
Hypopharynx	1.05 (0.40-2.74)	1.39 (0.55-3.49)
Larynx	0.60 (0.35-1.03)	1.33 (0.79-2.23)
Stage (#)		
I	1.00	-
II	1.02 (0.51-2.05)	-
III	1.27 (0.64-2.52)	-
IV	<b>2.25 (1.26-4.03)</b>	-
Treatment (§)		
Surgical	1.00	-
Surgical, radiation	0.64 (0.30-1.35)	-
Surgical, radiation, chemotherapy	1.32 (0.65-2.69)	-
<b>Cigarette smoking</b>		
Smoking status		
Never	1.00	1.00
Former	1.78 (0.77-4.15)	0.85 (0.45-1.61)
Current	1.54 (0.69-3.45)	1.32 (0.75-2.32)
Years of smoking		
Never smokers	1.00	1.00
<20	1.93 (0.73-5.12)	0.66 (0.26-1.71)
21-40	1.58 (0.70-3.55)	0.89 (0.47-1.57)
>40	1.32 (0.54-3.24)	<b>1.91 (1.00-3.68)</b>
Cigarettes per day		
Never smokers	1.00	1.00
<20	1.54 (0.69-3.43)	1.04 (0.59-1.84)
>20	1.78 (0.77-4.10)	1.31 (0.72-2.39)
<b>Alcohol drinking</b>		
Drinking status		
Never	1	1.00
Former	0.69 (0.27-1.75)	1.87 (0.85-4.13)
Current	0.84 (0.43-1.65)	1.31 (0.68-2.53)
Drinks per day (#)		
Never drinkers or <1	1.00	1.00
1-2	1.43 (0.44-4.66)	0.86 (0.46-1.63)
>2	0.82 (0.25-2.68)	1.40 (0.81-2.44)

Text in bold indicates statistically significant risk factors. HR: hazard ratio; CI: confidence interval.

(# ) More than 5% of the data were missing.

(§ ) The three most common types of cancer treatment were reported. 10% (n = 83) of the information is missing.

a HR adjusted by age, stage.

b HR adjusted by age

**Table 4**

Effects of the alcohol dehydrogenase polymorphisms (ADH) rs1229984 and rs1573496 on head and neck cancer (HNC) prognosis

	Death from HNC and oesophageal cancer (TOT/deaths 702/215)	Death from alcohol-related cancer (TOT/deaths 702/224)	Recurrence (TOT/recurrence 586/149)	SPC (TOT/SPC 611/117)	Second primary alcohol-related cancers (TOT/SPC 613/160)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
<b>ADH1B rs1229984</b>					
GG	1.00	1.00	1.00	1.00	1.00
GT/TT	0.67 (0.42-1.08)	0.64 (0.40-1.03)	1.20 (0.74-1.96)	0.58 (0.28-1.20)	0.40 (0.10-1.72)
<b>ADH7 rs1573496</b>					
CC	1.00	1.00	1.00	1.00	1.00
C/GG	0.90 (0.61-1.31)	0.88 (0.60-1.28)	0.67 (0.40-1.13)	1.25 (0.75-2.08)	1.57 (0.70-3.50)

SPC: second primary cancer; HR: hazard ratio; CI: confidence interval; TOT: total.

**Fig. 1**

Kaplan-Meier unadjusted overall 5-year survival by head and neck cancer site

