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Clinical features and prognostic factors in patients with head and neck cancer: Results from a multicentric study

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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.
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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.

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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 for 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

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