

## EPIDEMIOLOGY AND AETIOLOGY OF HEAD AND NECK SQUAMOUS CELL CARCINOMA

GRANITA MUHAXHERI<sup>1</sup>, DRAGANA GABRIĆ<sup>2</sup> and VANJA VUČIĆEVIĆ BORAS<sup>2</sup>

<sup>1</sup>Department of Peridontology, University of Prishtina, Republika Kosovo

<sup>2</sup>Department of Oral Medicine, School of Dentistry, University of Zagreb, Croatia

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### Summary

**Introduction:** It was expected at least in Western countries that incidence of head and neck cancers (HNSCC) should become lower due to the propaganda against smoking. However, the expected decrease in HNSCC was not achieved in many countries. Tobacco and alcohol consumption are known as a major risk factors for development of HNSCC. It is well known that 15-20% of HNSCC are linked to HPV infection, however, some authors reported coexistence with other viruses as well. In the Eastern countries paan (betel nut), ghutka, that have been also linked to the development HNSCC. However, lately HNSCC have been linked to the low vegetable and fruit intake, vitamin deficiencies, coinfection with other viruses, certain genetic syndromes and occupational exposure. Therefore, the aim of this study is to review recent literature regarding epidemiology and other risk factors in the development of HNSCC.

**Methods:** Pubmed was searched in the past two years in order to find out novelties regarding epidemiology and aetiology for HNSCC and 34 papers were included.

**Results and Conclusion:** The results of this review paper show that smoking is a major contributing factor especially with alcohol both being dosed and time dependent in the development of HNSCC. Unhealthy diet, decrease in vitamin intake especially folate, C and E vitamin and occupational exposure were seen in the diseased. In about one fourth of the patients infection with HPV has been noticed, and in some coinfection with other viruses such as Epstein Barr, cytomegalovirus and HIV. Obviously genetic predisposition exists but also correlation with certain genetic syndromes such as Fanconi's anaemia and Bloom syndrome.

**KEY WORDS:** *head and neck cancer, risk factors, smoking, alcohol consumption, HPV, nutrients.*

### EPIDEMIOLOGIJA AND ETIOLOGIJA PLOČASTOG KARCINOMA GLAVE I VRATA

#### Sažetak

**Uvod:** Očekivalo se barem u Zapadnim zemljama kako će incidencija karcinoma glave i vrata biti manja uslijed propagande protiv pušenja. Ipak, očekivano smanjenje u incidenciji karcinoma glave i vrata nije postignuto u mnogim zemljama. Pušenje i konzumacija alkohola su glavni faktori rizika za nastanak karcinoma glave i vrata. Dobro je poznato da je 15-20% karcinoma glave i vrata povezao s HPV infekcijom, doduše, neki autori su izvijestili i o koegzistenciji s drugim virusima također. U istočnim zemljama paan (betel nut), ghutka su također povezani s nastankom karcinoma glave i vrata. Ipak, nedavno je karcinom glave i vrata povezan s rijetkim unosom povrća i voća, deficitom vitamina, koinfekcijom s drugim virusima, određenim genetskim sindromima i radnim okolišem. Stoga je cilj ovog istraživanja bio pregledati noviju literaturu s obzirom na epidemiologiju i druge rizične faktore u nastanku karcinoma glave i vrata.

**Metode:** Pubmed je pretražen u zadnje dvije godine kako bi se ustanovilo novosti vezane uz epidemiologiju i etiologiju karcinoma glave i vrata te su 34 rada uključena.

**Rezultati i zaključci:** Rezultati ovog preglednog rada pokazuju kako je pušenje najvažniji faktor koji doprinosi nastanku karcinoma glave i vrata uz konzumiranje alkohola, a što ovisi o dozi i vremenu izloženosti. Nezdrava prehrana,

smanjeni unos vitamina, posebice folata, C i E vitamina i radni okoliš se ustanove u oboljelih. U oko četvrtine pacijenata je ustanovljena infekcija s HPV virusom, a u nekih i koinfekcija s drugim virusima poput Epstein Barrovog, citomegalovirusa i HIV-a. Očito genetska predispozicija postoji ali i korelacija sa određenim genetskim sindromima poput Fankonijeve anemije i Bloomovog sindroma.

KLJUČNE RIJEČI: *karcinom glave i vrata, faktori rizika, pušenje, konzumacija alkohol, HPV, prehrana*

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## INTRODUCTION

Epidemiology of head and neck cancers (HNSCC) varies throughout the world. In the last five years in Croatia, 450 new diagnosed cases of HNSCC have been registered annually with 350 deaths caused by HNSCC.

Tobacco smoking and chewing together with alcohol consumption are main contributors in the development of head and neck cancers. Decrease in the incidence of HNSCC has been expected due to the propaganda against smoking. In some countries paan (betel nut), ghutka or khat chewing as well as marijuana intake have been linked with HNSCC (1). Apart from these major risks, it is well known that inadequate oral hygiene, bad oral habits and teeth or prosthodontic related causes might lead to the development of HNSCC. Furthermore, inadequate diet and vitamin intake as well as occupational exposure have been recognized as a possible contributing factor in the development of HNSCC (2, 3, 4). It has been recognized that 15-20% HNSCC are correlated with HPV, as these patients do not have standard risk factors such as smoking and alcohol consumption (5). Lately, coexistence of HPV viruses together with Epstein-Barr virus or cytomegalovirus has been implicated in the development of HNSCC (6). Apart from these, certain genetic syndromes such as Fanconi's anaemia and Bloom syndrome have been linked with HNSCC (7).

The aim of this study was to search Pubmed in the past two years regarding epidemiology and aetiology of HNSCC.

## METHODS

Search of Pubmed regarding published papers in the last three years upon epidemiology and etiology of HNSCC was performed and 34 articles were found.

## RESULTS AND DISCUSSION

### EPIDEMIOLOGY OF HNSCC

Epidemiological data regarding HNSCC vary throughout the world. It has been expected that due to the smoking ban policies in some countries, decrease in HNSCC occurrence will be achieved. However, data are controversial. In some of these countries increasing incidence of head and neck cancer (HNSCC) in young adults has been reported. Weatherspoon et al. (8) reported changes in the incidence of oral cancer based on anatomic location and demographic factors over time the United States. About 75,468 incident oral cancer cases were diagnosed from 2000 to 2010. The tonsil was the most frequently diagnosed anatomic subsite (23.1%). An increasing incidence trend was observed for cancers in the oropharyngeal region, in contrast to decreasing trend seen in the oral cavity region (8). Zhang et al. (9) included 28 studies involving 13,830 patients with head and neck cancer in the past 45 years. The same authors (9) reported that the increased alcohol and tobacco consumption trends increased the risk of head and neck cancer over the past 45 years. Tobacco consumption was found to be a stronger risk factor for head and neck cancer than alcohol consumption (9). Katzel et al. (10) performed a cohort study from 1995-2010 (n = 2.2 million annual members) and identified 1,383 human papillomavirus (HPV)-related and 1,344 HPV-unrelated oral cavity and oropharyngeal cancer cases. The observed increasing HPV-related cancer rates are most evident among nonsmokers, whereas the decreasing HPV-unrelated cancer rates are least evident among younger individuals, nonsmokers, and those without an alcohol abuse history (10). Winn et al. (11) included 35 studies who have pooled their data at 25 500 patients with head and neck cancer (i.e., cancers of the oral cavity, oropharynx, hypopharynx, and larynx) and 37 100 controls. The same authors (11) have confirmed

that tobacco use and alcohol intake are key risk factors of these diseases. Other risk factors include short height, lean body mass, low education and income, and a family history of head and neck cancer. Zhang et al. (12) analysed 177 population-based cancer registries distributed in 28 provinces of China with a total of 175,310,169 populations and accounting for 13.01% of the overall national population in 2011. The estimate of new cases diagnosed with oral cancer was 39,450 including 26,160 males and 13,290 females. The overall incidence rate for oral cancer was 2.93/100,000. The estimated number of oral cancer deaths of China in 2011 was 16,933. Oral cancer accounted for 0.80% of all cancer deaths. In addition, the incidence and mortality rates were increased by the raising of ages (12). Hertrampf et al. (13) reported that the annual incidence of oral cancer is about 13,000 in Germany. The same authors (13) reported that men are 2.5-times more likely than women to be diagnosed and 3-times more likely to die from this tumour. Incidence and mortality in women increased slightly during the last decade, while incidence and mortality in men remained stable at a high level. While a decline was observed for younger age groups, an increase was seen in the elderly ones. This is probably due to the efforts in non-smoker protection in recent years (11). Toporcov et al. (14) pooled data from 25 case-control studies and conducted separate analyses for adults  $\leq 45$  years old and  $>45$  years old. The young group of cases had a higher proportion of oral tongue cancer (16.0% in women; 11.0% in men) and unspecified oral cavity / oropharynx cancer (16.2%; 11.1%) and a lower proportion of larynx cancer (12.1%; 16.6%) than older adult cases. The proportions of never smokers or never drinkers among female cases were higher than among male cases in both age groups. Positive associations with HNSCC and duration or pack-years of smoking and drinking were similar across age groups. However, the attributable fractions (AFs) for smoking and drinking were lower in young when compared with older. A family history of early-onset cancer was associated with HNSCC risk in the young (23.2%), but not in the older adults (2.2%). Differences in HNSCC aetiology according to age group may exist. The lower AF of cigarette smoking and alcohol drinking in young adults may be due to the reduced length of exposure due to the lower age (14). Guntinas-Lichius et al. (15)

analysed data of 6291 patients with primary HNSCC from the Thuringian cancer registry. Crude incidences of HNC increased significantly from 13.77 to 20.39 between 1996 and 2011. The same authors (15) concluded that the incidence of oral cancer is significantly increasing. Bagnardi et al. (16) analysed a total of 572 studies, including 486 538 cancer cases. The same authors concluded that alcohol increases risk of cancer of oral cavity and pharynx, oesophagus, colorectum, liver, larynx and female breast. Jayasekara et al. (17) observed a dose-dependent association between lifetime alcohol intake and the risk of upper aerodigestive tract cancer (UADT) with an intake of  $\geq 40$  g/day of alcohol and for a 10 g/day increment in intake. A positive association with baseline alcohol intake a 10 g/day increment in intake was found to be a slightly weaker predictor of risk than lifetime intake (17). Sharma et al. (18) reported that upper aero-digestive tract (UADT) cancers in North East India represent 37.6% of all cancers in both sexes, accounting for 53.3% in males and about 27.5% in females of the total cases. There were 5,638 cases registered during the last four years of the study (2008-2011) accounting for 56.7% (3,198/5,638) of the total in males and 43.3% (2,440/5,638) in females. The male: female ratio was 1.31: 1.00. Cancer of the oesophagus was most common in both sexes, with most appreciable gender variation for tongue and hypopharynx, presumably reflecting differential exposure to risk factors (18). Krishna et al. (19) reported significant associations between OSCC at middle age and male subjects. Cases with both habits of tobacco chewing and smoking were at a higher risk for OSCC than just tobacco chewing, duration of risk habits also emerged as a responsible factor for the development of carcinoma. The buccal mucosa was the most common (35.5%) affected oral site (19). Sharp et al. (20) analysed all HNSCC which were diagnosed from 1994 to 2009 from the National Cancer Registry Ireland who were classified by smoking status at diagnosis. Follow-up had been performed for 5 years, i.e. until December 31, 2010. In total, 5,652 head and neck cancers were included. At diagnosis, 24% were never smokers, 20% ex-smokers, and 56% current smokers. Compared with never smokers, current smokers had a significantly raised death rate caused by cancer. A significantly increased cancer-related death rate was seen at current smokers with oral cavity, pha-

ryngeal, and laryngeal cancers. The association was stronger in surgically treated patients. Neither radiotherapy nor chemotherapy modified the effect of smoking. Patients with head and neck cancer who smoke have a significantly increased cancer death rate (20).

## AETIOLOGY OF HEAD AND NECK CANCERS

### *BODY HEIGHT AND BODY MASS INDEX*

Study performed by Etemadi et al. (2) comprised of 218,854 participants aged 50 to 71 years who were cancer free at baseline (1995 and 1996). Until year 2006, 779 incident HNSCC occurred: 342 in the oral cavity, 120 in the oro- and hypopharynx, 265 in the larynx, 12 in the nasopharynx, and 40 at overlapping sites. There was an inverse correlation between HNSCC and body mass index, which was almost exclusively among current smokers and diminished as initial years of follow-up were excluded. Direct correlation with waist-to-hip ratio particularly for cancers of the oral cavity was seen. Height was also directly associated with total HNSCC, and oro- and hypopharyngeal cancers. The same authors concluded that this finding was probably due to the tobacco smoking (2).

### *VITAMIN AND CERTAIN FOOD INTAKE*

Edefonti et al. (3) reported that greater vitamin E intake from foods may lower HNSCC risk, although the authors were not able to explain the heterogeneity observed across studies or rule out certain sources of bias. Study was performed on the sample of 5959 HNSCC cases and 12 248 controls. The same authors in another study (21) reported that the inverse association of vitamin C intake from foods with HNSCC may reflect a protective effect on these cancers; however, the authors cannot rule out other explanations. The objective of the study of Cittadini et al. (22) was to analyze beef consumption, conjugated linoleic acid (CLA) and n-3 fatty acid (FA) serum concentration and their relation to salivary gland tumors (SGT). A questionnaire on non-nutritional risk factors and validated food frequency questionnaire were applied in 20 SGT and 20 control (Co) patients. Serum oleic and linolenic FAs showed a significant negative association with SGT. Fanidi et al. (23) measured plasma levels of vitamins B2, B6, B9 (folate), B12, and methionine and homocys-

teine in pre-diagnostic plasma samples and analyzed in relation to HNSCC and esophagus cancer risk, as well as post-diagnosis all-cause mortality in 385,747 participants. After controlling risk factors, study participants with higher levels of homocysteine had elevated risk of HNSCC. A slight decrease in HNC risk was also seen among subjects with higher levels of folate. Plasma concentrations of the other investigated biomarkers did not display any clear association with risk or survival (23).

Galeone et al. (24) analysed 5,127 cases and 13,249 controls and concluded that the highest OPC risk was observed in heavy alcohol drinkers with low folate intake as compared to never/light drinkers with high folate. Maasland et al. (25) reported that consumption of vegetables and fruits (or of specific groups of them) may protect against HNSCC and its subtypes. Study was performed on 120,852 participants and after 20.3 years of follow-up, 415 cases of HNC (131 OCC, 88 OHPC, 3 oral cavity/pharynx stayed unspecified or overlapping and 193 LC) were seen.

It has been speculated that tea intake might reduce risk of HNSCC development. Zhang et al. (26) performed a literature search and included 14 studies upon this topic. The same authors (26) reported that tea consumption was associated with decreased risk of oral cancer, while no association was detected with oral/pharyngeal, pharyngeal, or laryngeal cancer.

### *OTHER MEDICAL CONDITIONS*

It has been postulated that gastroesophageal reflux plays a role in the etiology of head and neck squamous cell carcinomas (HNSCC). Papagerakis et al. (27) evaluated 596 patients with HNSCC and reported a significant associations between the use of histamine receptor-2 antagonists (H2RA) and proton pump inhibitors (PPI), alone or in combination, and various clinical characteristics as well. The findings in this large cohort study indicated that routine use of antacid medications may have significant therapeutic benefit in patients with HNSCC. Helby et al. (28) measured plasma total IgE in 37 747 individuals from the general population, and the participants were followed prospectively for up to 30 years. During the mean follow-up of 7 years, a first cancer was diagnosed in 3454 participants. The multivariable ad-



justed hazard ratio for a 10-fold higher level of IgE was 1.05 [95% confidence interval for any cancer, 0.44 for chronic lymphocytic leukemia (CLL), 0.53 for multiple myeloma, 1.54 for other non-Hodgkin lymphoma, 1.38 for cancer of the oral cavity and pharynx, and 1.12 for lung cancer. High levels of plasma total IgE were associated with low risk of CLL and possibly of multiple myeloma, without convincing evidence for high risk of any cancer type (28).

### OCCUPATIONAL HAZARD

Carton et al. (29) included 296 squamous cell carcinomas of the head and neck in women and 775 controls. An elevated risk was observed for working proprietors working for 10 years or more with a significant trend with duration of employment. Elevated but non-significant risk was observed for street vendors, bakers, welders and flame cutters. The same authors (29) suggested a role of occupational exposures in the development of HNSCC cancer in women. Reijula et al. (4) studied a cohort of 16,134 male and 81,838 female waiters from Denmark, Finland, Iceland, Norway and Sweden. During the follow-up period from 1961 to 2005, they found that 19,388 incident cancer cases were diagnosed. Among male waiters highest incidence for cancers in the pharynx, oral cavity and tongue was seen. In female waiters, cancers of the larynx, oral cavity and lung was noticed. The risk of cancer among waiters was higher than in the general population. The elevated incidence in some cancer sites can likely be explained by higher alcohol consumption, the prevalence of smoking and occupational exposure to tobacco smoke (4). Petrochemical plant maintenance workers are exposed to various carcinogens such as benzene and metal fumes. Koh et al. (30) analysed data of 14 698 male workers registered in a regional petrochemical plant maintenance workers union during the years 2002-2007 and concluded upon potential association between oral and pharyngeal cancers and temporary maintenance jobs in the petrochemical industry.

### HPV and HNSCC

Within HNSCC, the highest prevalence of HPV-DNA is found in the oropharynx (soft palate, base of the tongue, tonsillar area and posterior pharynx). However, the role of HPV in the devel-

opment of solely oral cancer is controversial. Patients with HNSCC and HPV infection have better prognosis, treatment response and survival when compared to the HNSCC patients without HPV infection. Furthermore, patients with HNSCC who smoke and drink alcohol but also have HPV infection have better prognosis in comparison to the ones without HPV infection (31). It is thought that HPV starts cancerogenesis but also is considered as a buffer of other factors which lead to the cancer. It has been recognized that certain sexual practices such as oro-genital and oro-anal sex are highly correlated with HPV positive cancers (32). HPV prevalence depended upon tumour location and significantly more HPV has been found in oropharynx and larynx. Within males with HNSCC more HPV was noticed when compared to the females.

### *Co-infection with other viruses*

Sand and Jalouli (33) reported that besides HPV, Epstein-Barr virus (EBV) and herpes simplex virus 1 (HSV-1) might play a role in the HNSCC cancerogenesis. Polz-Gruszka et al. (6) identified EBV in 57.5%, HSV-1 in 7.5% and cytomegalovirus (CMV) in 10% of 80 patients with oral squamous cell cancer having also HPV. Co-infection of two viruses was noticed in 30% of the studied patients, most frequently being EBV and HPV (15%). Beachler et al. (34) concluded that incidence of oropharyngeal cancer (both HPV positive and negative) was significantly increased in HIV positive patients when compared to the general population probably as a result of immunosuppression.

### *Coexistence with certain syndromes*

Van Monsjou et al. (7) reported that in some patients genetic syndromes like Fanconi's anaemia and Bloom syndrome may play a role in the development of HNSCC.

Conclusion: The results of this review paper show that smoking is a major contributing factor especially with simultaneous alcohol consumption (both being dosed and time dependent) in the development of HNSCC. Unhealthy diet, decrease in vitamin intake especially folate, C and E vitamin and occupational exposure were seen in the diseased. In about one fourth of the patients infection with HPV has been noticed, and in some coinfection with other viruses such as Epstein Barr,

cytomegalovirus and HIV. Obviously genetic pre-disposition exists but also correlation with certain genetic syndromes such as Fanconi's anaemia and Bloom syndrome.

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*Author's address: Vanja Vučićević Boras, Department of oral medicine, School of dentistry, University of Zagreb, Gundulićeva 5, 10000 Zagreb, Croatia. email: boras@sfzg.hr*

