MINI-REVIEW

Potential Role of the Alcohol and Smoking in the Squamous Cell Carcinoma of the Head And Neck: Review of the Current Literature and New Perspectives

Anna Zygogianni[1*], George Kyrgias[2], Kyriaki Mystakidou[1], Christos Antypas[1], John Kouvaris[1], Christos Papadimitriou[3], Vassilis Armonis[4], Hassan Alkati[5], Vassilis Kouloulias[6]

Abstract

Alcohol and tobacco are responsible for a very large proportion of chronic disease and some tumors in particular may be the result of interactions between the two risk factors. The present systematic literature review was conducted to judge combined effects of alcohol drinking and tobacco, as well as and genetic polymorphisms on alcohol-related cancer risk. We can conclude that the interaction of smoking and alcohol significantly increases the risk for aero-digestive cancers. Unfortunately, little is known about mechanisms and details of interaction with regard to disease outcomes, which is why particular questions must be targeted in future research efforts.

Keywords: Alcohol consumption - tobacco smoking - cancer - head and neck - factor interactions

Asian Pacific J Cancer Prev, **12**, 339-344

Introduction

Squamous cell carcinomas (SCC) encompass at least 90% of all oral malignancies (Benken et al., 2003; Warnakulasuriya et al., 2008). Oral cancer holds the eighth position in the cancer incidence worldwide, with epidemiologic variations between different geographic regions (it is the third most common malignancy in south-central Asia).(World Health Organization 2003). In the US, oral squamous cell carcinomas (OSCC) represents 2%-4% of the annually diagnosed malignancies, being responsible for 8,000 deaths every year (US Department of Health and Human Services 2000). At the time of the diagnosis, 36% of patients have a localized disease, 43% a regionally spread disease and 9% present distant metastasis. In some western European countries, such as Belgium, Denmark, Greece, Portugal and Scotland, there has been an upward trend in the incidence of OSCC. Increasing mortality rates have been observed for at least two decades in Eastern Europe, where OSCC represents a real public health issue (La Vecchia et al., 2004).

OSCC implies quite significant mortality and morbidity rates, and despite the vast amount of research and although the advances which were accomplished in the field of oncology and surgery, the mortality rates remain unchanged. This fact motivates the search of factors with prognostic relevance in order to better tailor the individual management of OSCC patients. The purpose of this article is to list and discuss some of these factors, focusing on some of the most promising ones too (US Department of Health and Human Services, 2000; Benken et al., 2003; Warnakulasuriya et al., 2008).

Literature Survey

A web-based search for all types of articles published was initiated using MEDLINE/PubMed, with key words such as oral cancer, alcohol consumption, genetic polymorphisms and tobacco smoking. The sites of specialized scientific journals in the areas of oral medicine and oncology were also used. We give an overview of published studies on the combined effects of alcohol drinking, smoking and polymorphisms in genes for alcohol dehydrogenase (*ADH*), aldehyde dehydrogenase (*ALDH*), cytochrome P450 2E1, and methylene-tetrahydrofolate reductase on the risk of alcohol-related cancer. Other available data are insufficient or inconclusive, highlighting the need for additional studies. The search was restricted to articles published in English, with no publication date restriction (last update December, 2010).

Patient Related factors

There are no prognostic differences between males and

*[1]1st Radiology Department, [6]2nd Radiology Department, Medical School, Aretaieion Hospital, Kapodistrian University Hospital, Athens, [2] Radiotherapy Department, Medical School, Thessalia University, [3]Medical Oncology Unit, ALEXANDRAS General Hospital, [4]IKA Medical Oncology Unit, Athens, Greece, [5]Syrian Medical Center, Damascus, Syria *For correspondence : annazygo1@yahoo.gr*

females (Lo et al., 2003; Ocharoenrat et al., 2003) although some authors have reported lower survival rates in females, attributed to the delay in seeking medical care and the lower acceptance of treatment (Petti et al., 2008). The correlation of prognosis with age seems controversial and some authors show no relationship between them, whereas others demonstrate worse prognosis in older patients (Al-Rajhi et al.,2000; Lo et al., 2003; O-charoenrat et al., 2003; Ribeiro et al., 2003; Petti et al., 2008).

In patients with lower socioeconomic status and education, the results showed a worse prognosis, most likely because of a poorer oral hygiene and a more difficult access to medical care (Petti et al., 2008).

Furthermore it seems highly likely that diagnostic delays raise the probability of higher tumour growth and spread and consequently the prognosis is aggravated. However, an extensive review concerning OSCC pointed out that the available data fail to demonstrate this thesis, a fact partially attributed to methodological insufficiencies of the published studies. Another possible theory is that patients with more hostile tumours develop symptoms earlier and they seek medical attention sooner; nevertheless, these patients still have to face a more grievous outcome, because these malignancies display a more aggressive biologic behaviour (Allison et al., 1998).

Alcohol Consumption

The effect of alcohol-drinking on oral cancer risk has been reviewed by several studies. Ethanol has been blamed for causing cancer of the upper aerodigestive tract (ie, of the oral cavity, pharynx, or oesophagus) (Baan et al., 2007; Institut National du Cancer and Réseau National Alimentation Cancer Recherche, 2007; World Cancer Research Fund, 2007). The metabolism of ethanol is mainly done in the liver. The main enzymes which oxidize ethanol into acetaldehyde consist of alcohol dehydrogenases (ADH) and the cytochrome P450 2E1 (CYP2E1, a member of the cytochrome P450 superfamily). (Leiber et al., 1997; Villard et al., 1998; Seitz et al., 2007; Chi et al., 2009) As a result, acetaldehyde is changed into acetate by aldehyde dehydrogenases (ALDH).

We review published studies of consequences of diverse polymorphic genes and alcoholic beverages on the risk of alcohol-related cancer in the upper aerodigestive tract.

ADH1B - ADH1C

Human alcohol dehydrogenase (ADH) displays various molecular forms resulting in amino acid sequence differences. Bosron WF et al studied the gene that encodes the alcohol-metabolizing enzyme ADH1B which has a polymorphism that might modulate alcohol-oxidizing capability and drinking behavior (Bosron et al., 1986). In addition they studied the *ADH1C* gene which carries two alleles, *ADH1C*1* and *ADH1C*2*. The isoenzymes encoded by the *ADH1C*1* allele metabolize ethanol into acetaldehyde 2·5-times shifter than those encoded by the *ADH1C*2* allele (Bosron et al., 1986; Hoog et al., 1986). In the ones of white ethnic origin, neither allele prevails. By contrast, the frequency of the *ADH1C*1* allele is 75-90% in Africans and 85-100% in Asian populations (Brennan et al., 2004; Quertemont et al., 2004).

Asakage et al and Hiraki A et al observing Asian populations found out a significantly higher risk of cancer of the upper aerodigestive tract, oral cavity or oropharynx and hypopharynx in moderate or heavy drinkers carrying the *ADH1B*1* allele or *ADH1C*1/*2* or *ADH1C*2/*2* genotypes (Asakage et al., 2007; Hiraki et al., 2007). In particular, a gene–environment interaction between *ADH1B* polymorphism and alcohol-drinking was significant (p=0·035), this is to say that the risk of cancer of the upper aerodigestive tract in heavy drinkers with a *ADH1B*1* allele was higher than in heavy drinkers carrying the *ADH1B*2* allele. The same thing happens with the *ADH1C*1/*2* or *ADH1C*2/*2* allele (Yokoyama et al., 2002; Yang et al., 2005; 2007; Chen et al., 2006).

A recent multicentre study carried out in European countries, with a total number 811of cases of upper aerodigestive cancer , discovered a protective effect of the *ADH1B*2* allele in drinkers compared with *ADH1B*1*. (Hashibe et al., 2006) These results are in agreement with the conclusions of a pooled analysis of three multicentre case-control studies (n=3876) of ADH, which was made by Hashibe et al (2008) alcohol-drinking and risk of cancer of the upper aerodigestive tract. An interaction between alcohol consumption and *ADH1C* genotype to be vital. A significantly increased risk was noted for European moderate drinkers with *ADH1C*1/*1* genotype compared with *ADH1C*2* allele carriers, by contrast (Peters et al., 2005).

The study by Zavras et al., (2002) showed an increased risk of oral cancer for *ADH1C*1* heavy drinkers of white ethnic origin, but the interaction was not important. In the study by Bouchardy et al , the consequences of *ADH1C*1/*1* genotype and lifetime alcohol consumption in white individuals were associated with an increased risk (Bouchardy et al., 2000).

The only available study focusing on risk of larynx cancer in people of White ethnic origin by Risch A et al did not identified a significant modification of risk with ADH1B and ADH1C genotype and alcohol consumption (Bouchardy et al., 2000; Risch et al., 2003).

To sum up, the results obtained for *ADH1B* polymorphisms do not concord with the so-called acetaldehyde hypothesis that the *ADH1B*1* allele (which encodes a less-active enzyme, leading to lower acetaldehyde exposure) should decrease the risk of cancer in drinkers. On the contrary, a decreased risk of cancer of the upper aerodigestive tract was recorded in drinkers who carried the *ADH1B*2* allele that codes for the more-active enzyme. The increased risk for *ADH1B*1* homozygotes might result from an absence of alcohol flushing, enhanced by the vulnerability to drinking and the lifetime exposure to acetaldehyde, increasing the potential for so-called binge-drinking, and longer exposure of the mucosa to ethanol. What is more in isoenzymes encoded by ADHIC*1 allele the results were ambiguous as far as the risk of head and neck cancer in White- African and Asian population is concerned (Druesne-Pecollo et al., 2009).

ALDH2

ALDH2 mutant allele has been identified, which is a result from the substitution of glutamate to lysine at residue 487. The alleles that encode the active and inactive subunits are *ALDH2*1* and *ALDH2*2*, respectively (Brennan et al., 2004).

Diverse studies for cancer of the upper aerodigestive tract, (Yang et al., 2005; 2007; Chen et al., 2006) showed an increased risk for (Matsui et al., 2001; Hashibe et al., 2006; Asakage et al., 2007; Hiraki et al., 2007; Seitz et al., 2010) Asians who were moderate or heavy drinkers and carriers of the *ALDH2*2* allele. The *ALDH2*2* allele which has reduced activity, decreases the elimination of acetaldehyde. Furthermore, patients with *ALDH2* deficiency have increased acetaldehyde levels in serum and in saliva than the ones with *ALDH2*1/*1* genotype (Seitz et al., 2007).

CYP2E1

In white populations the highest risks of oral cavity or pharyngeal cancer were observed among the heaviest drinkers, with a significant 7·2-times increased risk for carriers of *CYP2E1 c2* genotype and a significant 2·5-times increased risk for those of *CYP2E1 c1/c1* genotype compared with moderate drinkers with *c1/c1* genotype. However, the small number of carriers of *CYP2E1* variant alleles has obstructed the interaction analysis (Yu et al., 1995; Hildesheim et al., 1997; Lee et al., 1997; Bouchardy et al., 2000; Choi et al., 2003; Risch et al., 2003 Yang et al., 2005; Gatta et al., 2006; Gao et al., 2007).

MTHFR

MTHFR plays a crucial part in folate metabolism. It has been demonstrated by diverse studies the relation between *MTHFR* polymorphism , alcohol consumption and cancer risk (Chen et al., 1996; Ma et al., 1997; Slattery et al., 1999; Kim et al., 2004; Le Marchand et al., 2005; Suzuki et al., 2007). The study by Suzuki T et al has shown that Asian heavy drinkers with *MTHFR TT* genotype had a significantly decreased risk of head and neck cancer compared with *CT* and *CC* genotypes.

Capaccio and co-workers have shown that moderate drinkers of white ethnic origin who are either double heterozygous or double homozygous for *MTHFR* mutations at residues 677 and 1298 had a higher risk of glottic, supraglottic, and oropharyngeal cancer (Capaccio et al., 2005).

Alcohol plus Tobacco

Alcohol and cigarette smoking are connected to each other (Burling et al., 1988; Di Franza et al., 1990; Miller et al., 1998; Kohn et al., 2003). The prevalence of smoking among substance abusers is about two to three times the one of the general population. Alcoholism is regarded to be 10 times more common among smokers than among non-smokers (Marks et al., 1997).

The concomitant use of tobacco and alcohol contributes to an increased risk of several malignancies, especially head and neck cancers. If we compare men who drink and smoke simultaneously with the ones who do not, we can conclude that the first ones have more possibilities to develop head and neck cancers (Blot et al., 1988; Vaillant et al., 1991; Talamini et al., 2002; Znaor et al., 2003).

The risk for a second primary tumour in patients with a previous upper aerodigestive tract tumour is augmented by alcohol and smoking (Do et al., 2003).

Henning et al have reported that xenobiotic metabolizing enzymes such as arylamine *N*-acetyltransferases (NAT1 and NAT2) genotypes are associated with laryngeal cancer risk (Henning et al., 1999).

Also mutations in the p53 gene are observed in patients addicted to alcohol and smoking (Miyazaki et al., 2002; Morita et al., 2002).nIn addition Wallstrom P et al have observed that the high alcohol consumption and smoking in combination with glutathione-S-transferases M1 (GSTM1) null genotype is associated with the appearance of cancer risk (Wallstrom et al., 2003). Rodriquez M. et al have reported that the combination between smoking and loss of methylguanine-DNA-methyltransferase (MGMT) protein expression contributes to an early detection in oral carcinogenesis (Rodriquez et al., 2007).

Conclusions

Despite the fact that most of the OSCC is usually aetiologically linked with tobacco and/or alcohol , there are patients who clearly develop OSCC in the absence of exposure to these, and in the absence of any obvious predisposing genetic defect (Herrero et al., 2003).

Human papillomavirus (HPV) in oral cancers suggests that HPV may play a similar role in transforming the oral epithelia with the presence of this virus in all cervical cancers as it has been referred in Xavier et al., (2007).

The mechanism with which epithelium is transformed has to do with the mutation of p53 and DNA tumour viral pathogenesis. High-risk HPV18 was detected in the tonsils of 3 benign controls without a previous cancer history. Others have reported that HPV16 presence is related to oral malignancy in 95% of HPV associated HNSCC. The detection of HPV18 in this subset was interesting, as HPV18 does not share the same oral oncogenic potential as HPV16 (Dahlstrom et al., 2003; D'Souza et al., 2007; Pintos et al., 2008).

Andrews et al., (2009) have claimed that the infection with HPV increases the risk of the development of oropharyngeal squamous cell carcinoma, in patients who do not smoke or drink. The use of prophylactic HPV vaccines based on virus-like particles (VLPs) have been successfully tested in premalignant cervical disease (Koutsky et al., 2002). The presence of HPV in orophayngeal cancers may warrant the use of vaccination in boys as well as in girls 9-15 years of age, for oral cancer prophylaxis.

Despite the attainments already achieved concerning OSCC diagnosis and therapy, mortality and morbidity rates are still exceedingly high, challenging the available methods of prognosis assessment and encouraging the search for new and better markers (Zygogianni et al., 2011). The immense diversity found in the field of clinical oncology must be considered from two main perspectives: the biologic distinctiveness of each patient and the biologic

distinctiveness of each malignancy. In practical terms, the factors with greater consensual influence on disease outcome include disease staging, extracapsular spread, tumour thickness and resection margin free of disease. In the future, better results in clinical oncology appear to rely on improved understanding of tumour molecular biology.

Acknowledgments

The authors would like to thank the university students who participated in this study.

References

Allison P, Locker D, Feine JS, et al (1998). The role of diagnostic delays in the prognosis of oral cancer: a review of the literature. *Oral Oncol*, **34**, 161-70.

Al-Rajhi N, Khafaga Y, El-Husseiny J, et al (2000). Early stage carcinoma of oral tongue: prognostic factors for local control and survival. *Oral Oncol,* **36**, 508-14.

Andrews E, Seaman WT, Webster-Cyriaque J (2009). Webster-Cyriaque, Oropharyngeal carcinoma in non smokers and non drinkers: a role for HPV. *Oral Oncol,* **45**, 486-91.

Asakage T, Yokoyama A, Haneda T, et al (2007). Genetic polymorphisms of alcohol and aldehyde dehydrogenases, and drinking, smoking and diet in Japanese men with oral and pharyngeal squamous cell carcinoma. *Carcinogenesis,* **28**, 865-74.

Baan R, Straif K, Grosse Y, et al (2007). Carcinogenicity of alcoholic beverages. *Lancet Oncol,* **8**, 292-3.

Beenken SW, Urist MM, et al (2003). Head and neck tumors. in: l.w way and G.M. doherty, editors, *Current surgical diagnosis and treatment* (11th ed.), lange medical books/ McGraw-Hill, New York, 282-29.

Blot WJ, McLaughlin JK, Winn DM, et al (1988). Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res,* **48**, 3282-7.

Bouchardy C, Hirvonen A, Coutelle C, et al (2000). Role of alcohol dehydrogenase 3 and cytochrome P-4502E1 genotypes in susceptibility to cancers of the upper aerodigestive tract. *Int J Cancer,* **87**, 734-40.

Bosron WF, Li TK (1986). Genetic polymorphism of human liver alcohol and aldehyde dehydrogenases, and their relationship to alcohol metabolism and alcoholism. *Hepatology*, **6**, 502-10.

Brennan P, Lewis S, Hashibe M, et al (2004). Pooled analysis of alcohol dehydrogenase genotypes and head and neck cancer: a HuGE review. *Am J Epidemiol,* **159**, 1-16.

Burling TA, Ziff DC (1988). Tobacco smoking: a comparison between alcohol and drug abuse inpatients. *Addict Behav,* **13**, 185-90.

Capaccio P, Ottaviani F, Cuccarini V, et al (2005). Association between methylenetetrahydrofolate reductase polymorphisms, alcohol intake and oropharyngolaryngeal carcinoma in northern Italy. *J Laryngol Otol*, **119**, 371-6.

Chen J, Giovannucci E, Kelsey K, et al (1996). A methylenetetrahydrofolate reductase polymorphism and the risk of colorectal cancer. *Cancer Res,* **56**, 4862-4.

Chen YJ, Chen C, Wu DC, et al (2006). Interactive effects of lifetime alcohol consumption and alcohol and aldehyde dehydrogenase polymorphisms on esophageal cancer risks. *Int J Cancer,* **119**, 2827-31.

Chi AC, Appleton K, Henriod JB, et al (2009). Differential induction of CYP1A1 and CYP1B1 by benzo[a]pyrene in oral squamous cell carcinoma cell lines and by tobacco smoking in oral mucosa. *Oral Oncol*, **45**, 980-5.

Choi JY, Abel J, Neuhaus T, et al (2003). Role of alcohol and genetic polymorphisms of CYP2E1 and ALDH2 in breast cancer development. *Pharmacogenetics,* **13**, 67-72.

Dahlstrom KR, Adler-Storthz K, Etzel CJ, et al (2003), Human papillomavirus type 16 infection and squamous cell carcinoma of the head and neck in never-smokers: a matched pair analysis. *Clin Cancer Res,* **9**, 2620-6.

Di Franza JR, Guerrera MP (1990). Alcoholism and smoking. *J Stud Alcohol,* **51**, 130-5.

Do KA, Johnson MM, Doherty DA, et al (2003). Second primary tumors in patients with upper aerodigestive tract cancers: joint effects of smoking and alcohol (United States). *Cancer Causes Control,* **14**, 131-8.

Druesne-Pecollo N, Tehard B, Mallet Y, et al (2009). Hercberg S and Latino-Martel P, alcohol and genetic polymorphisms: effect on risk of alcohol-related cancer. *Lancet Oncol*, **10**, 173-80.

D'Souza G, Kreimer AR, Viscidi R, et al (2007). Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med,* **356**, 1944-56.

Gao CM, Takezaki T, Wu JZ, et al (2007). CYP2E1 Rsa I polymorphism impacts on risk of colorectal cancer association with smoking and alcohol drinking. *World J Gastroenterol,* **13**, 5725-30.

Gattá GJF, De Carvalho MB, Siraque MS, et al (2006). Genetic polymorphisms of CYP1A1, CYP2E1, GSTM1, and GSTT1 associated with head and neck cancer. *Head Neck,* **28**, 819-26.

Hashibe M, Boffetta P, Zaridze D, et al (2006). Evidence for an important role of alcohol- and aldehyde-metabolizing genes in cancers of the upper aerodigestive tract. *Cancer Epidemiol Biomarkers Prev,* **15**, 696-703.

Hashibe M, McKay JD, Curado MP, et al (2008). Multiple ADH genes are associated with upper aerodigestive cancers *Nat Genet,* **40**, 707-9.

Henning S, Cascorbi I, Munchow B, et al (1999). Association of arylamine N-acetyltransferases NAT1 and NAT2 genotypes to laryngeal cancer risk. *Pharmacogenetics,* **9**, 103-11.

Herrero R, Castellsague X, Pawlita M (2003). Human papillomavirus and oral cancer: the international agency for research on cancer multicenter study. *J Natl Cancer Inst,* **95**, 1772-83.

Hildesheim A, Anderson LM, Chen CJ, et al (1997). CYP2E1 genetic polymorphisms and risk of nasopharyngeal carcinoma in Taiwan. *J Natl Cancer Inst,* **89**, 1207-12.

Hiraki A, Matsuo K, Wakai K, et al (2007). Gene-gene and gene-environment interactions between alcohol drinking habit and polymorphisms in alcohol-metabolizing enzyme genes and the risk of head and neck cancer in Japan. *Cancer Sci,* **98**, 1087-91.

Hoog JO, Heden LO, Larsson K, et al (1986). The gamma 1 and gamma 2 subunits of human liver alcohol dehydrogenase, cDNA structures, two amino acid replacements, and compatibility with changes in the enzymatic properties. *Eur J Biochem,* **159**, 215-8.

Institut national du cancer and réseau national alimentation cancer recherche (2007). *Alcool et risque de cancers. Etat des lieux des données scientifiques et recommandations de santé publique*, INCa, Boulogne-Billancourt.

Kim DH, Ahn YO, Lee BH, et al (2004). Methylenetetrahydrofolate reductase polymorphism, alcohol intake, and risks of colon and rectal cancers in Korea. *Cancer Lett,* **216**, 199-205.

Kohn CS, Tsoh JY, Weisner CM, et al (2003). Changes in smoking status among substance abusers: baseline characteristics and

abstinence from alcohol and drugs at 12-month follow-up. *Drug Alcohol Depend*, **69**, 61-71.

Koutsky LA, Ault KA, Wheeler CM, et al (2002) A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med,* **347**, 1645-51.

La Vecchia C, Lucchini F, Negri E, et al (2004). Trends in oral cancer mortality in Europe. *Oral Oncol*, **40**, 433-9.

Lee HS, Yoon JH, Kamimura S, et al (1997). Lack of association of cytochrome P450 2E1 genetic polymorphisms with the risk of human hepatocellular carcinoma. *Int J Cancer,* **71**, 737-40.

Le Marchand L, Wilkens LR, Kolonel LN, et al (2005). The MTHFR C677T polymorphism and colorectal cancer: the multiethnic cohort study. *Cancer Epidemiol Biomarkers Prev*, **14**, 1198-203.

Lieber CS (1997). Cytochrome P-4502E1: its physiological and pathological role. *Physiol Rev*, **77**, 517-44.

Lo WL, Kao SY, Chi LY, et al (2003). Outcomes of oral squamous cell carcinoma in Taiwan after surgical therapy: factors affecting survival. *J Oral Maxillofac Surg,* **61**, 751-8.

Ma J, Stampfer MJ, Giovannucci E, et al (1997). Methylenetetrahydrofolate reductase polymorphism, dietary interactions, and risk of colorectal cancer. *Cancer Res,* **57**, 1098-102.

Marks JL, Hill EM, Pomerleau CS, et al (1997). Nicotine dependence and withdrawal in alcoholic and nonalcoholic ever-smokers. *J Subst Abuse Treat,* **14**, 521-7.

Matsuo K, Hamajima N, Shinoda M, et al (2001). Gene-environment interaction between an aldehyde dehydrogenase-2 (ALDH2) polymorphism and alcohol consumption for the risk of esophageal cancer. *Carcinogenesis,* **22**, 913-6.

Miller NS, Gold MS (1998). Comorbid cigarette and alcohol addiction: epidemiology and treatment. *J Addict Dis,* **17**, 55-66.

Miyazaki M, Ohno S, Futatsugi M, et al (2002). The relation of alcohol consumption and cigarette smoking to the multiple occurrence of esophageal dysplasia and squamous cell carcinoma. *Surgery*, **131**, S7-13.

Morita M, Saeki H, Mori M, et al (2002). Risk factors for esophageal cancer and the multiple occurrence of carcinoma in the upper aerodigestive tract. *Surgery,* **131**, S1-6.

O-charoenrat P, Pillai G, Patel S, et al (2003). Tumor thickness predicts cervical nodal metastases and survival in early oral tongue cancer. *Oral Oncol*, **39**, 386-90.

Peters ES, McClean MD, Liu M, et al (2005). The ADH1C polymorphism modifies the risk of squamous cell carcinoma of the head and neck associated with alcohol and tobacco use. *Cancer Epidemiol Biomarkers Prev,* **14**, 476-82.

Petti S (2008). Lifestyle risk factors for oral cancer. *Oral Oncol,* **45**, 340-50.

Pintos J, Black MJ, Sadeghi N, et al (2008). Human papillomavirus infection and oral cancer: a case-control study in Montreal, Canada. *Oral Oncol,* **44**, 242-50

Quertemont E (2004). Genetic polymorphism in ethanol metabolism: acetaldehyde contribution to alcohol abuse and alcoholism. *Mol Psychiatry,* **9**, 570-81.

Ribeiro KCB, Kowalski LP, MRDO (2003). Perioperative complications, comorbidities, and survival in oral or oropharyngeal cancer. *Arch Otolaryngol Head Neck Surg*, **129**, 219-28.

Risch A, Ramroth H, Raedts V, et al (2003). Laryngeal cancer risk in Caucasians is associated with alcohol and tobacco consumption but not modified by genetic polymorphisms in class I alcohol dehydrogenases ADH1B and ADH1C, and glutathione-S-transferases GSTM1 and GSTT1. *Pharmacogenetics*, **13**, 225-30.

Rodriquez M, Acha A, Ruesga M, et al (2007). Loss of expression of DNA repair enzyme MGMT in oral leukoplakia and early oral squamous cell carcinoma. a prognostic tool? *Cancer Lett,* **245**, 263-8.

Seitz HK, Stickel F (2007). Molecular mechanisms of alcohol-mediated carcinogenesis. *Nat Rev Cancer*, **7**, 599-612.

Seitz HK, Stickel F (2010). Acetaldehyde as an underestimated risk factor for cancer development: role of genetics in ethanol metabolism. *Gene Nutr*, **5**, 121-8.

Slattery ML, Potter JD, Samowitz W, et al (1999). Methylenetetrahydrofolate reductase, diet, and risk of colon cancer. *Cancer Epidemiol Biomarkers Prev,* **8**, 513-8.

Suzuki T, Matsuo K, Hasegawa Y, et al (2007). One-carbon metabolism-related gene polymorphisms and risk of head and neck squamous cell carcinoma: case-control study. *Cancer Sci,* **98**, 1439-46.

Talamini R, Bosetti C, La Vecchia C, et al (2002). Combined effect of tobacco and alcohol on laryngeal cancer risk: a case-control study. *Cancer Causes Control*, **13**, 957-64.

U.S. Department of Health and Human Services, (2000). *Oral health in America: a report of the Surgeon General-executive summary*, US department of health and human services, national institute of dental and craniofacial research, national institutes of health, rockville (MD), 1-13.

Vaillant GE, Schnurr PP, Baron JA, et al (1991). A prospective study of the effects of cigarette smoking and alcohol abuse on mortality. *J Gen Intern Med,* **6**, 299-304.

Villard PH, Seree EM, Re JL, et al (1998). Effects of tobacco smoke on the gene expression of the Cyp1a, Cyp2b, Cyp2e, and Cyp3a subfamilies in mouse liver and lung: relation to single strand breaks of DNA. *Toxicol Appl Pharmacol*, **148**, 195-204.

Wallstrom P, Frenkel K, Wirfalt E, et al (2003). Antibodies against 5-hydroxymethyl-2`-deoxyuridine are associated with lifestyle factors and GSTM1 genotype: a report from the malmo diet and cancer cohort. *Cancer Epidemiol Biomarkers Prev*, **12**, 444-51.

Warnakulasuriya S (2008). Global epidemiology of oral and oropharyngeal cancer. *Oral Oncol*, **45**, 309-16.

World Cancer Research Fund and American Institute for Cancer Research (2007). *Food, nutrition, physical Activity, and the prevention of cancer: a global perspective*, AICR, Washington DC.

World Health Organization (2003). *The World Oral Health Report 2003*, World Health Organization, Geneva, 6-7.

Xavier Bosch, Silvia de Sanjosé (2007). The epidemiology of human papillomavirus infection and cervical cancer. *Dis Markers,* **23**, 213-27.

Yang CX, Matsuo K, Ito H, et al (2005). Esophageal cancer risk by ALDH2 and ADH2 polymorphisms and alcohol consumption: exploration of gene-environment and gene-gene interactions. *Asian Pac J Cancer Prev,* **6**, 256-62.

Yang SJ, Wang HY, Li XQ, et al (2007). Genetic polymorphisms of ADH2 and ALDH2 association with esophageal cancer risk in southwest China. *World J Gastroenterol*, **13**, 5760-4.

Yokoyama A, Kato H, Yokoyama T, et al (2002). Genetic polymorphisms of alcohol and aldehyde dehydrogenases and glutathione S-transferase M1 and drinking, smoking, and diet in Japanese men with esophageal squamous cell carcinoma. *Carcinogenesis*, **23**, 1851-9.

Yu MW, Gladek-Yarborough A, Chiamprasert S, et al (1995). Cytochrome P450 2E1 and glutathione s-transferase M1 polymorphisms and susceptibility to hepatocellular carcinoma. *Gastroenterology,* **109**, 1266-73.

Zavras AI, Wu T, Laskaris G, et al (2002). Interaction between a single nucleotide polymorphism in the alcohol dehydrogenase 3 gene, alcohol consumption and oral cancer risk. *Int J Cancer,* **97**, 526-30.

Znaor A, Brennan P, Gajalakshmi V, et al (2003). Independent and combined effects of tobacco smoking, chewing and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men. *Int J Cancer,* **105**, 681-6.
Zygogianni A, Kyrgias G, Karakitsos P, et al (2011). Oral squamous cell cancer: early detection and the role of alcohol and smoking. *Head Neck Oncol,* **3**, 2.