Etiology of head and neck cancer (C01–14, C32) in Central and South America

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Tobacco smoking and alcohol consumption

Cigarette smoking and alcohol consumption are the main factors that have consistently been associated with the incidence of and mortality from head and neck cancers [1, 2]. In a recent pooled analysis that used international data from 1981 to 2007, Wyss et al. [3] found that cigarette smoking was strongly related to an increased risk of head and neck cancers (odds ratio [OR] for ever-smokers vs never-smokers, 3.5; 95% confidence interval [CI], 3.24–3.70). The odds ratios for cigarette smoking (ever-smokers vs never-smokers) were higher in Europe (OR, 5.83; 95% CI, 5.07–6.71) and South America (OR, 4.54; 95% CI, 3.89–5.31) than in North America (OR, 2.09; 95% CI, 1.89–2.32). An independent analysis of the effects of smoking cigarettes, cigars, or pipes compared with never smoking showed similar elevated risks for smoking cigarettes only (OR, 3.93; 95% CI, 3.67–4.22), for smoking cigars only (OR, 3.49; 95% CI, 2.58–4.73), and for smoking pipes only (OR, 3.71; 95% CI, 2.59–5.33).

In a case–control study conducted in Argentina, Brazil, and Cuba in 1998, Szymańska et al. [4] showed that tobacco smoking was associated with an increased risk of head and neck cancer compared with not smoking after adjusting for sex, age, centre, education, gram–years of alcohol, and consumption of fruit and cruciferous vegetables. The odds ratios were 5.49 (95% CI, 4.06–7.41) for cancer of the oral cavity and oropharynx and 7.44 (95% CI, 5.30–10.45) for cancer of the hypopharynx and larynx; for hypopharyngeal and laryngeal cancer, higher risks were found among current smokers compared with never-smokers (OR, 11.14; 95% CI, 7.72–16.08). When the analysis was restricted to never-drinkers, the positive association between tobacco smoking and the risk of hypopharyngeal and laryngeal cancer was maintained (OR, 6.97; 95% CI, 3.89–12.47).

In a matched case–control study conducted in Uruguay between 1988 and 2000, de Stefani et al. [5] found that tobacco smoking was positively associated with cancers of the oral cavity (OR for ever- vs never-smokers, 7.7; 95% CI, 4.2–18.0) and pharynx (OR for ever- vs never-smokers, 18.6; 95% CI, 7.4–46.3) cancers. In a matched case–control study of squamous cell cancer of the larynx conducted in Uruguay, de Stefani et al. [6] reported that the association with tobacco smoking (never-smokers vs ever-smokers) differed markedly between subsites (OR for

supraglottic cancer, 16.7; 95% CI, 5.1– 54.4; OR for glottic cancer, 8.2; 95% CI, 2.9–23.1). Similar differences between the two subsites were found among current smokers for intensity of smoking (number of cigarettes per day) in heavy smokers (OR for supraglottic cancer, 40.4; 95% CI, 11.9–137.4; OR for glottic cancer, 16.4; 95% CI, 5.4–50.1) and duration of smoking (years) in long-term smokers (OR for supraglottic cancer, 46.4; 95% CI, 13.1–164.9; OR for glottic cancer, 13.6; 95% CI, 4.5–41.0).

In a matched case–control study conducted in Cuba, a country with a high prevalence of smoking (43.1% among men and 26.5% among women) [7], Garrote et al. [8] estimated that 82% (95% CI, 72– 91%) of oral cancer cases in 2000 were attributable to tobacco smoking alone and 19% to smoking cigars or pipes only. In Cuba in 1995 and 2007, 82% and 84% of laryngeal cancers in men and 78% and 54% of those in women, respectively, were estimated to be attributable to smoking; similarly, 93% and 94% of oral cavity and pharyngeal cancer deaths occurring in men and 93% and 82% of those occurring in women were estimated as being attributable to smoking in these two years, respectively [9].

The incidence and mortality trends for oral, pharyngeal, and laryngeal cancers described above partially mirror the course of the tobacco epidemic described for Latin American and Caribbean countries [10]. However, no conclusion can be drawn due to the lack of complete long-term information on smoking trends for most of the countries.

In Europe, North America, and Latin America, alcohol consumption has consistently been associated with an increased risk of developing head and neck cancers [11]. However, variations in drinking patterns, the types of beverage and the duration of exposure may affect risk assessments within the different regions. In the case–control study conducted in Argentina, Brazil, and Cuba, Szymańska et al. [4] showed that ever-drinkers had an increased risk of developing head and neck squamous cell carcinomas (HNSCC) compared with never-drinkers with adjusted odds ratios of 2.50 (95% CI, 1.91–3.26) for the hypopharynx and larynx and 4.62 (95% CI, 3.39–6.28) for the oral cavity and oropharynx. Differences in cancer risks were seen according to alcohol consumption and type of alcohol. Among ever-drinkers, a very strong effect of aperitifs and spirits was found compared with that of beer (OR for oral cavity and oropharynx, 3.99; 95% CI, 2.60–6.14; OR for hypopharynx and larynx, 2.73; 95% CI, 1.77–4.21). Dose–response relationships were also evident for both oral cavity–oropharyngeal and hypopharyngeal–laryngeal sites compared with never-drinkers.

In a case–control study conducted in Brazil, Schlecht et al. [12] reported that the risk of pharyngeal and laryngeal cancers was higher in drinkers than in non-drinkers (relative risk [RR], 2.8; 95% CI, 1.9–4.0) independently of smoking consumption and that the risk varied according to the levels of consumption, the type of alcoholic beverage and the percentage of alcohol intake. A higher consumption (> 100 kg cumulative lifetime exposure) of hard liquors and cachaça was strongly associated with cancers of the mouth (RR, 6.9; 95% CI, 2.8–17.1 for hard liquors; RR, 4.5; 95% CI, 2.2–9.2 for cachaça).

In a case–control study in Cuba, Garrote et al. [8] found a 5–6fold higher risk of developing oral cavity and oropharyngeal cancer among heavy drinkers (≥ 70 drinks

per week) of hard liquor compared with non-drinkers (OR, 5.73; 95% CI, 1.77–18.52) and reported that consumption of hard liquors accounted for 70% of the total alcohol intake in this population. Similarly, in the case–control study conducted in Uruguay, de Stefani et al. [5] showed that ever-drinkers had a higher risk of pharyngeal cancers (OR, 4.3; 95% CI, 2.9–6.4) and oral cancers (OR, 3.3; 95% CI, 2.2–4.8) than never-drinkers. In addition, the cumulative dose of alcohol (alcohol–years) and consumption of wine were associated with a higher risk of pharyngeal carcinomas than that of oral carcinomas. In a subsequent analysis, de Stefani et al. [6] found that current and ever drinkers had an approximately 3–4-fold risk of supraglottic and about a 2-fold risk of glottic carcinoma compared with never-drinkers; similar differences by laryngeal cancer subtype were observed for wine consumption (> 60 mL of ethanol per day) and total ethanol consumption (> 60 mL of ethanol per day) compared with never-drinkers.

The interaction between tobacco use and alcohol consumption and the risk of head and neck cancers has been explored in several studies [1, 4, 11]. In a pooled analysis of 18 case–control studies, Hashibe et al. [11] reported that the overall risk of head and neck cancers for the joint effect of tobacco use and alcohol consumption in Latin America was almost 10 times as high as that of never use (OR, 9.78; 95% CI, 5.36–17.85). The independent effects were 1.07 (95% CI, 0.49–2.36) for alcohol alone and 3.35 (95% CI, 1.69–6.65) for tobacco alone; thus the joint effect of tobacco use and alcohol consumption was greater than that expected under the multiplicative model for all head and neck cancers (Ψ = 2.68; 95% CI, 1.69–4.25).

Striking findings were reported by Garrote et al. [8] in Cuba where those who consumed the highest levels of alcohol (≥ 21 drinks per week) and smoked heavily (≥ 30 cigarettes per day) had a 111-fold (95% CI, 22.7–543.7-fold) risk of cancer of the oral cavity and oropharynx than non-consumers (multiplicative or supra-multiplicative effect); moreover, former drinkers who continued to smoke heavily (≥ 30 cigarettes per day) had a 33.6-fold (95% CI, 1.55–728.88-fold) risk of these cancers than never-users.

In Uruguay, de Stefani et al. [6] reported an interaction between the type of tobacco smoked (blond, mixed and white) and different levels of wine consumption on the risk of developing supraglottic and glottic cancers. They found that those who consumed the highest levels of alcohol (> 60 mL of ethanol per day) and smoked had an approximately 4–20-fold risk of developing supraglottic cancers than non-drinkers/smokers and null to weakly positive associations were observed for the joint effect of high levels of alcohol consumption and smoking on glottic cancers. These findings revealed an important and alarming effect of smoking and drinking behaviours in the Central and South American region, which emphasises the need to develop anti-smoking interventions and support abstention or moderation in alcohol drinking.

Human papillomavirus infection

Human papillomavirus (HPV) is associated with HNSCC and is strongly linked to oropharyngeal tumours [13]. HPV-related tumours represent a distinct epidemiological, biological, and clinical subset of head and neck cancers that are identified more frequently in younger subjects (aged < 60 years) [14]. Patients with

HPV-positive HNSCC appear to have a more favourable overall survival rate and respond better to treatment, particularly in the case of oropharyngeal tumours, than those with HPV-negative diseases [15–19]. Recent studies revealed that HPV-positive tumours constitute approximately 25% of all HNSCCs and that the prevalence is significantly higher for cancers of the oropharynx (35.6%; range, 11–100%) than for those of the oral cavity (23.5%; range, 40–80%) or larynx (24.0%; range, 0–100%), with HPV16, a high-risk subtype, being the predominant genotype found [20, 21]. However, the reported prevalence of HPV-related tumours suggests certain geographical differences [22–25] mostly due to the accompanying burden of tobacco- and alcohol-associated diseases in these tumours.

Data on the prevalence of HPV in the Central and South American region are sparse and only a few small studies are available (sample sizes ranging from 5 to < 250 cases) in which different HPV detection techniques were used. In Argentina, Brazil, and Cuba, the prevalence of HPV ranged from 0% to 19% in oropharyngeal cancers, from 0% to 78% in oral cavity cancers (including Mexico and Venezuela), and from 0.8% to 48.5% in hypopharyngeal and laryngeal cancers (including Chile) [26].

The prevalence of HPV16 in HNSCC was ascertained by the detection of both viral DNA and serum antibodies E6 and E7 in three case–control studies that included cases from Latin America (Argentina, Brazil, and Cuba) [27–29]; overall, Latin America had a lower prevalence (between 3.1% and 3.9%) of HPV16-related HNSCC than Europe and North America [30–32].

Regardless of the low prevalence in the region described in these studies, HPV16 E6 and E7 antibodies (which are generally considered to be markers of invasive HPV16-transformed tumours) were strongly associated with cancers of both the oropharynx (OR, 179; 95% CI, 35.8–899) and the hypopharynx/larynx (OR, 14.9; 95% CI, 2.92–76.1) [27]. The low prevalence of HPV16 found in these studies might reflect the low incidence rates of oropharyngeal cancer in the region; according to Cancer Incidence in Five Continents Volume X, the highest incidence rates (per 100 000) of tonsillar and other oropharyngeal tumours were 3.4 in São Paulo, 3.1 in Goiânia, Brazil, and 2.1 in Uruguay [33].

Exomic and genomic approaches have also revealed differences in the genetic landscapes of HPV-associated and HPV-negative HNSCCs [34–36]. HPV-positive tumours have distinctive patterns of somatic mutations, copy number alterations, and gene expression profiles compared with HPV-negative cancers [37]. HPV-related cancers have been purported to have an increased sensitivity to current treatments which resulted in a greater improvement in survival among patients with HPV-positive HNSCC compared with those who had HPV-negative tumours [19, 38]. HPV16 E6 and E6/E7 seropositivity in Central and South American cases has been associated with a reduction in overall death rates from oropharyngeal cancers [28].

The association between tobacco, alcohol consumption, HPV infection, and tumour site appears to be complex. The risks of combined exposures appear to be distinct according to the tumour site, suggesting that different molecular pathways are involved. The biological behaviour of an HPV-positive tumour may be altered by tobacco use [39]. Some evidence suggests that genetic alterations induced by tobacco-associated carcinogens may render HPV-positive tumours less responsive

to therapy and the likelihood of such genetic alterations appears to increase with the number of pack–years of tobacco smoking [40]. However, further studies are necessary to elucidate this complex interaction and define specific exposure-associated risks.

Recent evidence indicated that sexual behaviours are the means by which individuals with HPV-positive head and neck tumours are exposed to the virus [41, 42]. Various analyses indicated that the overall increased risk of cancers of the oropharynx, tonsil, and base of the tongue in the Central and South American region is associated with an increased number of both lifetime sexual partners and oral sex partners, although differences in risk were seen for specific subsites [27, 43].

Genetic susceptibility

Several genetic polymorphisms have been associated with the risk of HNSCC. Most of the genetic associations studied are related to single nucleotide polymorphisms in genes involved in metabolism, cell-cycle control, and alcohol metabolism [44]. The IARC-Latin America Multicentre study described associations with susceptibility to oral, pharyngeal, and laryngeal cancers for the alcohol dehydrogenase (ADH) variant genes *ADH1B* (rs1229984; $P = 0.002$), *ADH7 (*rs1573496; $P = 0.008$), and *ADH1C* (rs1693482; $P = 0.04$) [45]. The results showed that, while the *ADH1C* rs1693482 variant was associated with a moderate increase in risk for the above-mentioned cancers, both the *ADH1B* and *ADH7* variants conferred a protective effect that was dependent on the levels of alcohol consumption. Evidence of higher rates of alcohol metabolism has been are shown for the rs1229984 (*ADH1B*) G/A and A/A genotypes, providing support for the hypothesis that faster metabolism of ethanol reduces the duration of local exposure and may exert a protective effect [46]. The preventive biological effect of the *ADH7* variant is still unclear but suggests a role in alcohol metabolism.

In a large genome-wide association study that included the IARC-Latin America Multicentre study, McKay et al. [47] identified two additional novel variants: the 4q21 variant (rs1494961; $P = 1 \times 10^{-8}$) located in the *HEL308* DNA repair gene and the 12q24 variant (rs4767364, $P = 2 \times 10^{-8}$) located in a region close to the aldehyde dehydrogenase 2 (*ALDH2*) gene. However, the lack of large genome-wide association studies within Central and South America has limited an understanding of the genetic susceptibility of head and neck cancers in this region.

Mate consumption

The dried leaves and stem lets of the perennial tree *Ilex paraguariensis* (yerba mate, Jesuit's tea, chimarrão, or Paraguayan tea) are brewed and consumed as a beverage in many countries in South America, mainly in Argentina, southern Brazil, Paraguay, and Uruguay. Hot mate has been classified as being probably carcinogenic to humans from some evidence of its effect on the risk of HNSCC [48]. Repeated thermal injury in the mouth, pharynx, and larynx due to the consumption of very hot mate has been postulated to lead to cancer, and some of the chemical components of mate maybe carcinogens [49, 50].

The association between mate consumption and head and neck cancer has been evaluated in five case–control studies conducted in Central and South America, four of which showed statistically significant associations between mate drinking and oral and oropharyngeal cancer [51–55]. In a meta-analysis that included four of these case–control studies (oral cavity [*n* = 3] and tongue [*n* = 1]) that were conducted in Brazil and Uruguay, Desanayaki et al. [56] found that mate drinking was associated with a twofold increase in the risk of developing these malignancies (summary OR, 2.11; 95% CI, 1.39–3.19), although the results were heterogeneous (I = 67%) when compared with low/no consumption. The authors estimated that 16% of the cancer cases observed could be attributed to mate consumption, assuming that the controls represented the true prevalence of mate consumption in the population [56].

As reviewed by Loria et al. [50], all case–control studies conducted in South America found a higher risk for oral, oropharyngeal, and laryngeal cancers among mate consumers compared with no or low mate intake with a synergistic effect of exposures to mate, alcohol, and tobacco.

The carcinogenic mechanisms of mate consumption are still under evaluation; thermal injury and chemical carcinogens such as polycyclic aromatic hydrocarbons have been proposed as the main contributors. Several epidemiological studies in South America have consistently reported that drinking hot mate is a risk factor for oral, oropharyngeal, and laryngeal cancers [50] suggesting that a higher temperature per se might directly damage the oral mucosa or accelerate enzymatic reactions, including an enhancement of the effects of tobacco and alcohol. However, this hypothesis cannot validate the excess risk for cancer in other organs (urinary bladder, kidney, and lung) that do not come into direct contact with hot beverages. Evidence of the presence of polycyclic aromatic hydrocarbons in yerba mate leaves in both cold and hot infusions [57, 58] may account for the additional carcinogenic role of mate. Further studies, especially population-based case–control studies, might be necessary to evaluate more fully the role of mate consumption as a risk factor for HNSCC.

Nutritional factors

The World Cancer Research Fund evaluated the available evidence on diet and the risk of cancer and concluded that non-starchy vegetables, fruit, and foods containing carotenoids probably protect against cancers of the mouth, pharynx, and larynx, thus highlighting the importance of food and nutrition in the prevention of these malignancies [59]. In a recent pooled analysis of 22 case–control studies, Chuang et al. [60] also found that a high consumption of fruit and vegetables was inversely related to the risk of head and neck cancers (4th vs 1st quartile OR for fruit, 0.52; 95% CI, 0.43–0.62; 4th vs 1st quartile OR for vegetables, 0.66; 95% CI, 0.49–0.90). However, those who reported a high consumption (4th quartile) of red meat, beef, pork and processed meat had an approximately 37–48% higher risk of head and neck cancers than those who reported a low consumption (1st quartile). A few case–control studies in South America have studied the associations between diet, some nutrient-based dietary patterns, and the risk of head and neck cancers. Southern South America is a region with one of the highest global levels of red meat intake, particularly charcoal-grilled meat. A case–control study conducted in the southern, south-eastern, and mid-western regions of Brazil showed that charcoal-grilled red

meat was positively associated with oral and pharyngeal cancer (RR, 5.3; 95% CI, 1.9–15.0), but no association was detected with smoked meat [51]. A recent study in Uruguay based on four nutrient-derived patterns (meat-based, starchy, carotenoid, and fruit-based) showed that the meat-based pattern was positively associated with HNSCC (OR, 2.85; 95% CI, 1.81–4.15), whereas the fruit-based pattern had a protective effect (OR, 0.43; 95% CI, 0.27–0.63) [60, 61].

Occupational and environmental factors

Very few occupational studies have evaluated the risks of HNSCC in the Central and South American region. Andreotti et al. [62] evaluated the effect of several occupations in a hospital-based matched case–control study in men in the metropolitan area of São Paulo. After controlling for age, tobacco smoking, and alcohol consumption, men who were employed in vehicle maintenance shops and vehicle repairs had a 2-fold risk of cancers of the oral cavity and oropharynx compared with those who had never worked in these occupations (OR for oral cavity, 2.45; 95% CI, 1.14–5.27; OR for oropharynx, 2.10; 95% CI, 0.78–5.68). Among employees holding either of these occupations, the risk of malignancy increased with the length of employment (≥ 10 years). According to an IARC evaluation [63], it has been hypothesized that employees in these occupations may be exposed to possible carcinogens derived from gasoline fumes, diesel or anhydrous alcohol combustion, solvents, mists of lubricants, mineral oil, and strong acids, particles of insulating materials such as asbestos and glass fibres, metal and abrasive dust, aldehydes, welding fumes, and soot and therefore may be at increased risk of head and neck cancers.

Laryngeal carcinomas are causally associated with exposure to asbestos, although the precise mechanism that leads to carcinogenesis is still unknown [64]. Laryngeal cancer remains one of the occupational asbestos-related cancers in Argentina, Brazil, Colombia, and Mexico [65]. De Stefani et al. evaluated the risk of laryngeal cancer for several job titles and substances in a case–control study conducted in Uruguay and found strong positive associations with exposure to asbestos (OR, 2.4; 95% CI, 1.2–4.8), gasoline (OR, 1.7; 95% CI, 0.9–3.5), strong inorganic acids (OR, 1.8; 95% CI, 1.1–3.1), herbicides (OR, 2.4; 95% CI, 0.9–6.7), and fungicides (OR, 3.7; 95% CI, 1.3–10.7). Strong positive associations were observed among those working as a butcher (OR, 2.8; 95% CI, 1.1–7.2) and the risk of laryngeal cancer; when the cases were stratified by subsite, an elevated risk of glottic carcinomas was found in car assemblers (OR, 9.0; 95% CI, 1.6–50.5), mechanics (OR, 5.5; 95% CI, 1.3–23.5), electricians (OR, 5.7; 95% CI, 1.0–31.5), and metal workers (OR, 6.5; 95% CI, 1.1–38.9) [66].

An estimated 3 billion people worldwide cook and heat their homes with open fires; in the Central and South American region, the estimated percentage of households that use solid fuels for cooking in 2013 ranged from less than 5% in Argentina, Uruguay, and Venezuela to 53–64% in Nicaragua and Guatemala [67, 68]. In particular, wood stoves are very commonly used for cooking and heating in rural or remote areas among the Latin American region; their use is related to indoor pollution as they can produce high indoor concentrations of particulates, carbon monoxide, and other combustion-related pollutants [69]. In a case–control study conducted in Brazil, Pintos et al. [70] found an elevated risk of head and neck cancer for people exposed

to wood stove fumes (OR, 2.68; 95% CI, 2.2–3.3) after adjusting for tobacco smoking and alcohol consumption. These findings and the relative percentage of solid fuel use in some areas of the region suggest the need for additional studies that include a better exposure assessment and examine dose–response associations.

Oral health and hygiene

In general, a poor condition of the mouth, poor dentition, a lack of toothbrush use, and never having a dental check-up have been identified as risk factors for head and neck cancers, independently of tobacco use and alcohol consumption [71, 72]. A multicentre case–control study conducted in Argentina, Brazil, and Cuba showed that factors such as a poor condition of the mouth versus a good condition (OR, 1.91; 95% CI, 1.49–2.45) and never having a dental check-up versus an annual check-up (OR, 1.61; 95% CI, 1.18–2.20) were strongly related to the incidence of oral cavity, pharyngeal, and laryngeal cancer, independently of tobacco smoking and alcohol consumption [71]. A case–control study conducted in Brazil indicated an increased risk of oral cancer (RR, 2.3; 95% CI, 1.4–3.7) associated with infrequent use compared with daily use of a toothbrush [51]. In Central and South America, oral hygiene practices are dependent on access to sanitation facilities and dental health programmes, which may account for differences in associations between countries or within specific areas of a country.

Second primary cancers

Patients with HNSCC have a high risk of developing other cancers simultaneously or subsequently. Second primary cancers (SPCs) mostly develop in the oral cavity and pharynx, oesophagus, larynx, and lung, cancer sites that are also associated with tobacco smoking and alcohol consumption, and patients who develop an SPC have a decreased overall survival rate [73]. A multicentre study including data from 13 population-based cancer registries in Australia, Canada, Europe, and Singapore reported that the cumulative risk of an SPC 20 years after a head and neck cancer is approximately 36% for all sites combined. The study also reported that the highest standardized incidence ratios were found for second primary head and neck cancers that developed in cases diagnosed with a primary cancer at a younger age (< 56 years) (standardized incidence ratio, 14.9; 95% CI, 13.6–16.3). Increased risks of SPCs persisted 10 years after diagnosis of the first primary cancer, especially for SPCs in the head and neck, oesophagus, lung, other tobacco-related sites, and other alcohol-related sites [74]. Additional evidence supports that HNSCC patients who continue smoking and drinking alcohol have a higher risk of developing SPCs. Khuri et al. [75] reported a higher overall annual rate of SPC development among currently smoking HNSCC patients compared with non-smoking patients (5.7%; 95% CI, 4.6–7.2%). A case–control study conducted by Leon et al. [76] showed that the attributable risk of SPC in HNSCC patients who continued to smoke tobacco and/or consume alcohol after treatment was 33% (95% CI, 26–37%). The reported risks for the development of an SPC in patients who continued smoking or consuming alcohol were 2.9 (95% CI, 1.8– 4.1) and 5.2 (95% CI, 3.3–7.9), respectively. No study of this type has been conducted in the Central and South American region.

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