Etiology of oesophageal cancer (C15) in Central and South America

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Oesophageal squamous cell carcinoma (SCC) and adenocarcinoma (AC), the two main histological subtypes, have different etiologies and pathological characteristics [1–3]. Although several factors have been related to the risk of oesophageal carcinoma, this section only focuses on factors that are relevant for the Central and South American region.

Tobacco smoking and alcohol consumption

Exposure to tobacco smoke, including second-hand smoke, has been causally related to both subtypes of oesophageal cancer, while consumption of alcoholic beverages has been causally associated with SCC but has little or no association with AC of the oesophagus [4].

Cohort studies conducted in China, Japan, the Republic of Korea, the United Kingdom, and the USA (as cited in [4]) showed that smokers have an increased risk of developing oesophageal cancer than never-smokers and that the risk increases with the intensity of smoking (duration and number of packs per day). In a cohort study in the USA, Freedman et al. [5] reported that current smokers had a significantly increased risk of developing AC (hazard ratio [HR], 3.7; 95% confidence interval [CI], 2.20–6.22) and SCC (HR, 9.27; 95% CI, 4.04–21.29) than non-smokers. They also found strong positive associations between alcohol consumption (> 3 drinks per day vs 1 drink per day) and the risk of SCC (HR, 4.93; 95% CI, 2.69–9.03), but found no association with AC (HR, 1.10; 95% CI, 0.69–1.74). Pandeya et al. [6] estimated that 49% (95% CI, 38–60%) and 32% (95% CI, 25–40) of the oesophageal SCCs diagnosed in Australia between 2002 and 2005 were due to smoking and heavy alcohol consumption, respectively. Furthermore, more than 75% of the SCC burden in men could be attributed to smoking with heavy alcohol consumption; 36% (95% CI, 29–44%) of the SCCs in men but only 5% (95% CI, 2–10%) of those in women were due to smoking more than 30 pack–years and the consumption of more than 17 alcoholic drinks per week.

Castellsagué et al. [7] evaluated the combined effects of tobacco smoking and the consumption of alcoholic beverages on the risk of developing oesophageal SCC using data from five case–control studies conducted in Argentina, Brazil, Paraguay, and Uruguay and reported that the overall risk of oesophageal SCC for the joint effect of tobacco smoking and alcohol consumption was 8 times that of never use (odds ratio [OR], 8.0; 95% CI, 5.67–11.27). The odds ratios for independent effects were 1.95 (95% CI, 1.35–2.82) for tobacco alone and 1.75 (95% CI, 1.17–2.63) for alcohol use alone, and noticeable differences by sex were observed (OR, 17.0; 95%

CI, 8.36–34.78 for men; OR, 7.26; 95% CI, 3.68–14.33 for women). They also reported that the average amount of alcohol consumed per day, the duration of smoking, and the type of tobacco smoked were strongly connected with an increased risk of developing oesophageal SCC.

In the USA, Freedman et al. [5] estimated that “ever smoking” accounted for 77% (95% CI, 55–89%) of all oesophageal SCCs and 58% (95% CI, 38–72%) of all ACs diagnosed during 1995–1998, demonstrating a causal relationship between smoking and oesophageal cancer. In Cuba, Varona Pérez et al. [8] estimated that about 70% and 80% of the oesophageal cancer deaths reported in 1995 and 2007 could be attributed to smoking (79% and 82% among men and 76% and 69% among women, respectively).

Diet

Dietary factors have been suggested to play a role in the development of oesophageal cancer, although epidemiological evidence from cohort studies to support this claim is lacking [9]. For instance, *N*-nitroso compounds that are found in meat have been associated with risks for cancer [9, 10]. High consumption as compared with low consumption of red or processed meat was linked to an increased risk of oesophageal cancer in three meta-analyses of 18, 29, and 31 case–control studies [9–11]. A moderately positive association with the risk of oesophageal cancer was reported for daily consumption of processed meat (relative risk [RR], 1.57; 95% CI, 1.22–2.01 per 50 g per day) [10] and high consumption versus low consumption of barbecued meat (OR, 1.54; 95% CI, 1.25–1.191) [11].

In a meta-analysis, Salehi et al. [10] found that meat consumption was related to one oesophageal carcinoma subtype but not the other: high consumption versus low consumption of red meat was related to an increased risk of SCC (RR, 1.63; 95% CI, 1.00–2.63; *P* for heterogeneity = 0.001) while high consumption versus low consumption of processed meat was related to the risk of AC (RR, 1.37; 95% CI, 1.05–1.78; *P* for heterogeneity = 0.2). Similarly, Narang et al. [11] reported some associations between the type of meat consumed and oesophageal carcinoma subtype: overall meat consumption (red, processed, white, fish, and barbequed) was related to an increased risk of AC (OR, 1.12; 95% CI, 1.04–1.21) whereas that of processed meat was related to an increased risk of SCC (OR, 1.75; 95% CI, 1.28–2.38). In contrast, in a meta-analysis of nine case–control studies, Liu et al. [12] reported that having a diet with a “pattern typical of industrialized countries” (high intake of fat, animal, and processed foods and low intake of fruit, vegetables, and dietary fibre) was not associated with the risk of oesophageal SCC (OR, 1.29; 95% CI, 0.83–1.75). Discrepancies between these five meta-analyses may be explained by the number of studies included and the definitions employed in the respective analyses.

A diet with a “healthy pattern” (high consumption of fruit, fresh vegetables, dietary fibre, and antioxidants and low consumption of fat, dairy and processed foods, and red meat) has been inversely associated with the risk of SCC (OR, 0.36; 95% CI, 0.23–0.49) [12], while a high consumption of fish has been inversely connected to the risk of oesophageal AC (OR, 0.73; 95% CI, 0.55–0.95) [11]. In a meta-analysis of five case–control studies, Smolinska et al. [13] also reported that the frequent intake

of vegetables was related to a lower risk of oesophageal cancer (RR, 0.52; 95% CI, 0.38–0.71 for > 1 time per week; RR, 0.43; 95% CI, 0.32–0.58 for > 1 time per day) compared with less frequent vegetable intake. Similar results were reported by De Stefani et al. [14] in a meta-analysis of four case–control studies conducted in Uruguay (OR, 0.60; 95% CI, 0.49–0.74 for high vs low vegetable consumption; OR, 0.27; 95% CI, 0.19–0.38 for high vs low fruit consumption).

Thermal injury and maté consumption

Maté, a non-alcoholic infusion made from dry leaves of the tree *Ilex paraguariensis* (also known as yerba maté) [15–17], is commonly consumed in Argentina, Bolivia, Brazil, Chile, Ecuador, Paraguay, and Uruguay [16], mainly at very high temperatures, except in Paraguay and in south-eastern, north-eastern, and northern Brazil, where it is also consumed cold [16]. Although maté consumption has been linked with cancers of the oral cavity, pharynx, larynx, lung, kidney, and urinary bladder [18], its association with oesophageal cancer has been controversial [16, 19]. The World Cancer Research Fund/American Institute for Cancer Research concluded that evidence from case–control studies suggest that regular consumption of maté, as traditionally consumed in South America (drunk scalding hot through a metal straw), is a probable cause of oesophageal cancer [20]. The suggested mechanisms for the carcinogenicity of maté include thermal damage due to exposure to high-temperature infusions and exposure to some polycyclic aromatic compounds (i.e. benzo[*a*]pyrene) that are detected in both hot and cold maté infusions [15, 16, 18, 21].

A recent meta-analysis of nine case–control studies conducted in Argentina, Brazil, Paraguay, and Uruguay [22] revealed that those who had ever consumed maté had an increased risk of developing oesophageal SCC than never-users (OR, 2.57; 95% CI, 1.66–3.98), although heterogeneity was observed (I^2 = 65.4%; P = 0.002). Further subgroup analyses of studies that adjusted for tobacco smoking and alcohol consumption revealed a similar association between maté consumption and the increased risk of SCC (OR, 2.23; 95% CI, 1.15–4.35; heterogeneity I^2 = 48.9%; P = 0.141). Although this study revealed positive associations between maté consumption and the risk of oesophageal cancer, it did not consider the temperature of the maté (thermal injury). Therefore, these results could not determine whether this relationship is due to the chemical constituents of maté or residual confounding due to thermal injury.

Castellsagué et al. [23] evaluated the combined effects of the consumption (daily amount) and temperature of maté on the risk of developing oesophageal cancer using data from five case–-control studies conducted in Argentina, Brazil, Paraguay, and Uruguay. Heavy maté drinkers (> 1.50 L/day) had a 1.58-fold risk of developing oesophageal cancer compared with light drinkers (< 0.5 L/day) after adjusting for the effects of the temperature of the maté, tobacco smoking, and alcohol consumption (*P* for trend = 0.0006). Similar effects were reported for the temperature of the maté (OR, 1.62; 95% CI, 1.16–2.25) and consumption of other hot drinks (including coffee with milk and tea) on the risk of developing oesophageal cancer (OR, 2–4), although those who consumed maté at a very high temperature and were heavy drinkers had a higher risk of oesophageal cancer than light drinkers (OR, 4.14; 95% CI, 2.24–7.67). In this analysis, the consumption of very hot drinks (including maté) would

account for 10% and 12% of the incident oesophageal cancer cases in men and women, respectively (assuming that a causal relationship exists); these attributable risk estimates maybe overestimated because the consumption of other hot foods (i.e. soups) was not considered in the analysis. These results appeared to be consistent with the hypothesis that chronic thermal injury is associated with the increased risk of oesophageal cancer.

Recently, a Working Group convened by the International Agency for Research on Cancer (IARC) evaluated the carcinogenicity of drinking coffee, maté, and very hot beverages, as part of the IARC Monographs Programme. The Working Group found that drinking very hot (above 65 °C) beverages probably causes cancer of the oesophagus in humans. No conclusive evidence was found for drinking maté at temperatures that are not very hot or for drinking coffee [24].

Barrett's oesophagus

Obesity increases the risk of developing gastroesophageal reflux disease (GERD), an inflammatory condition in the distal oesophagus [25]. Approximately 10–15% of patients diagnosed with GERD develop Barrett's oesophagus [26], a metaplastic condition that may become dysplastic [27–29], which has been associated with a 30-fold increase in the incidence of oesophageal AC (as reviewed in [26]). Why only some people with Barrett's oesophagus develop neoplastic changes that progress to cancer while, in most people, it is a relatively benign condition throughout their life remains unclear (as reviewed in [26]).

In a cohort of 411 participants with Barrett´s oesophagus, the risk of oesophageal AC was higher among those who were older (HR, 1.03; 95% CI, 1.00–1.06 per year increase) and smoked (HR, 2.29; 95% CI, 1.04–5.07 per ≥ 36 pack–years); imprecise estimates were reported for several categories of body mass index and alcohol consumption after adjustment for age, sex, smoking, and non-steroidal anti-inflammatory drugs [26].

The decline in the prevalence of *Helicobacter pylori* infection in developed countries has been hypothesized to be responsible for the increased incidence of oesophageal AC [27, 30]. In a meta-analysis of 19 case–control studies, Islami et al. [31] found an inverse relationship between *H. pylori* infection and oesophageal AC (summary OR, 0.56; 95% CI, 0.46–0.68; I^2 = 15%) but not oesophageal SCC (summary OR, 1.10; 95% CI, 0.78–1.55; I^2 = 73%). A further analysis on eight studies revealed that colonization with cytotoxin-associated gene product A (CagA)-positive *H. pylori* strains was inversely associated with the risk of oesophageal AC (OR, 0.41; 95% CI, 0.28–0.62) but colonization with CagA-negative *H. pylori* strains was not (OR, 1.08; 95% CI, 0.76–1.53). These findings suggest that CagA-positive *H. pylori* strains may protect against oesophageal AC. However, in the evaluation of biological agents as human carcinogens, the International Agency for Research on Cancer concluded that (i) there is a lack of an association between *H. pylori* and an increased risk of oesophageal AC, and (ii) there is little evidence of an association between *H. pylori* and the risk of oesophageal SCC [32].

Other factors

Infections with human papillomavirus (HPV) have been suggested to play a role in the etiology of oesophageal cancer, although epidemiological evidence remains controversial [33–35]. Poor oral hygiene has been strongly related with an increased risk of SCC [1, 36, 37]. In a case–control study in Latin America (Argentina, Brazil, and Cuba), Guha et al. [37] reported that poor conditions of the mouth, a lack of tooth brushing and mouth washing, and having 6–15 teeth missing were strongly associated with an increased risk of SCC.

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