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Review

Lifestyle features as co-factors in head and neck cancer development

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Abstract

Ranked sixth most prevalent worldwide, head and neck cancers (HNCs) affect an increasing number of people. Several factors contribute to their occurrence, including genetic and epigenetic aberrations and lifestyle factors, including heavy smoking, alcohol consumption, chewing betel quid (Areca nuts), poor oral hygiene, consumption of pro-inflammatory foods, inhalation of chemical compounds, asbestos dust, and infections with HPV (human papillomavirus) and EBV (Epstein-Barr virus). Often diagnosed in advanced stages, they have a mortality rate of about 50% at 5 years and pose a serious threat to human health.

Keywords lifestyle factors, genetic aberration, pro-inflammatory food, chemical compounds

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Introduction

The head and neck region comprises the organs of the upper airways, the cranial cavity, the eyes, the ears, their appendages, the endocrine glands, the cervical spine, the cranial and cervical musculature, the blood vessels, including large blood vessels, the internal and external carotid arteries, the jugular veins and intracranial venous sinuses, the nerves and the integument covering them. Head and neck cancers (HNCs) refer to cancers occurring in the upper aerodigestive tract (nasal cavity; oral cavity with the lips, oral floor, hard palate, palatine veil, tongue, gums, and salivary glands; pharynx, with the nasopharyngeal, oropharyngeal and laryngopharyngeal/hypopharyngeal sectors, with the tonsils and the Eustachian tube communicating with the middle ear; larynx, with the vocal cords, glottis, and epiglottis). More than 90% of HNCs originate in the squamous cells lining the mucosa of the upper aerodigestive tract and are the sixth most common cancer, with more than half a million new cases annually [1] (in 2020, the number of new cases is estimated to be more than 900,000 [2, 3]).

The development of HNCs occurs in several stages, starting with the mutation of a single gene (usually *TP53*, Tumor Protein 53/Tumor Suppressor P53), continuing with the accumulation of somatic alterations in oncogenes (e.g., in the RAS–RAF–MEK–ERK and PIK3–AKT–mTOR signaling pathways), in tumor suppressor genes (e.g., *p16*/*INK4A*/*CDKN2AI*, Cyclin Dependent Kinase Inhibitor 2A) and in cell cycle regulatory genes (e.g., *CCND1*, Cyclin D1) and is favored by various lifestyle features, including heavy smoking (active and passive) and alcohol consumption, implicated in the etiology of about 72% of cases, chewing betel quid (Areca nuts), poor oral hygiene, consumption of pro-inflammatory foods (fried, smoked or roasted meat), inhalation of chemical compounds, asbestos dust, genetic factors [4-6], and HPV (human papillomavirus) and EBV (Epstein-Barr virus) infections, which are involved in the etiology of about 25% of cases (Fig. 1) [7, 8].

Although people with HNCs benefit from cytoreductive surgery, radiotherapy, and chemotherapy treatment when needed, and although metastasis is low (around 10%) due to diagnosis at advanced stages and high risk of recurrence, mortality at five years after diagnosis is high (around 50%), and is higher for primary laryngopharyngeal/hypopharyngeal tumors. Even after the cure, people with HNCs have a high lifetime risk of death, especially if they are smokers [6]. This paper aims to review the main unhealthy lifestyle factors (tobacco smoking, alcohol consumption, chewing Areca nuts (betel quid), and some eating habits) that can lead to HNCs.

Tobacco smoking

Tobacco (*Nicotiana tabacum* L.) is consumed as cigarettes or as chewing tobacco and snuff (generically referred to as smokeless tobacco, with the habit of smoking associated or not with alcohol consumption being present in about 90% of HNCs and ranking first in their etiology [9]. For regular smokers, the average risk of HNCs is ten times higher for men and five times higher for women than for non-smokers; for heavy smokers, it is up to 20 times higher than for non-smokers. Smoking dark tobacco also increases the risk of HNCs by 2.5 times compared to light smoking tobacco and 35 times compared to not smoking at all. Smoking cessation significantly reduces this risk without eliminating it, so that five years after quitting, the risk of oral and pharyngeal cancers falls by half [9, 10]. Cigarette smoke contains about 10^{10} particles/cm^3. About 95% of smoke aerosols are gases (mostly nitrogen, oxygen, monoxide, and carbon dioxide, but also other volatile compounds) and less than 5% particles [11]. 3044 compounds have been isolated from cigarette smoke, of which 69 have carcinogenic and genotoxic effects. These could be potentially responsible for inducing some of the chromosomal and gene abnormalities identified in smokers: (a) chromosomal aberrations; (b) sister chromatid exchanges; (c) micronuclei in peripheral lymphocyte nuclei; (d) carcinogen-nitrogen-base adducts in bronchial and laryngeal epithelial cells (absent in non-smokers) or in placental cells in smoking mothers, where they occur with a markedly higher frequency than placental cells of non-smoking mothers (16/17, in smokers compared to 3/16 in non-smokers) [12], and thus, significantly increasing the risk of upper aerodigestive and lung cancers, depending on the intensity and duration of the smoking habit [10]. The formation of adducts (complexes formed by a nitrogenous base and the carcinogen) is essential for carcinogenesis, as it determines the occurrence of point mutations, one of the leading causes of HNCs. The carcinogen is introduced from the external environment, as such, or can be derived by metabolism from a procarcinogen (e.g., benzo[a]pyrene, very common in anthropogenic environments), and, having an affinity for the nitrogenous bases in DNA, interacts with them, causing, in case of errors in the corrective mechanisms, the formation of point mutations (Fig. 1), including those in *TP53* gene [13]. The IARC classifies eleven compounds in cigarette smoke as having a very high carcinogenic risk to humans: 2-naphthylamine, 4-aminodiphenyl, benzene, vinyl chloride, ethylene oxide, arsenic, beryllium, nickel salts, chromium VI salts, cadmium salts and 210 polonium com-

pounds [12]. Since 3044 compounds, some with carcinogenic effects, have been isolated from tobacco, other forms of tobacco consumption intended for chewing and snuffing, wet and dry (so-called smokeless tobacco), are also risk factors for HNCs, with less relevance than smoking, mainly due to the antioxidants present in tobacco [14-18].

Carbon monoxide from cigarette smoke gets into the blood and, combined with hemoglobin in red blood cells, which has 200–280 times more affinity for carbon monoxide than oxygen, forms carboxyhemoglobin. This is more stable than carbohemoglobin (produced by combining carbon dioxide with hemoglobin) or oxyhemoglobin (produced by oxygenating hemoglobin) [19]. Increased carboxyhemoglobin concentration reduces the ability to discharge oxygen from the blood and its availability in tumors, and HNCs are known for the ease with which they enter hypoxia [20].

At the same time, nicotine induces vasoconstriction, exacerbating the hypoxic state [21]. Further, it increases glucose uptake, glycolysis, and acidification of the tumor micromedium, promoting HIF1A synthesis and initiating the angiogenesis pathway mediated by VEGFs [20] (Fig. 1).

Alcohol consumption

Frequent consumption of alcohol is a significant risk factor for the development of neoplasia in the upper aerodigestive region, especially in the oral, oropharyngeal, laryngopharyngeal and laryngeal regions, especially in association with smoking or consumption of other tobacco products [22-24]. Regardless of the association with tobacco, alcohol: (1) solubilizes some carcinogens and permeabilizes the plasma membranes of the epithelial cells, favoring the penetration of the former into the cytoplasm and nucleus; (2) can produce changes in the salivary glands, with increased saliva viscosity and insufficient moistening of the oral and oropharyngeal mucous membranes, which become sensitive to the action of some carcinogens; (3) exhibits toxic action on the epithelia; (4) reduces esophageal motility; (5) stimulates gastro-esophageal reflux, leading to local metaplasia; (6) activates cytochrome P450, which metabolizes it to acetaldehyde, which converts some procarcinogens (e.g. nitrosamines, aflatoxins, vinyl chloride, polycyclic hydrocarbons, etc.) into carcinogens, and which metabolizes retinoic acid, a light-signaling neuromodulator necessary for growth and for the regulation of gap junction-mediated coupling of retinal neurons, reducing its concentration and generating metabolites that interfere with cell cycle development and cellular hyper-regeneration; (7) promotes tumor processes, by impairing the cell-mediated immune surveillance and cytotoxic function of NK cells and by reducing tissue folate concentrations [24]. The first metabolite of alcohol, acetaldehyde, has carcinogenic effects by (1) affecting DNA synthesis; (2) interacting with some proteins, including enzymes involved in DNA repair and methylation, disrupting their functionality; (3) interacting directly with DNA, forming stable adducts and contributing to point mutations. Since alcohol metabolism to acetaldehyde can occur under the action of microorganisms in the oral cavity, the two compounds show conjugate effects in oral tumorigenesis. Based on these effects, in 2012, IARC included alcohol and acetaldehyde in the category of carcinogens for the human body, indicating that the impact of alcohol on the risk of HNCs depends more on the amount of alcohol consumed and not necessarily on its concentration in each drink [23-25]. The risk of HNCs decreases by 15% five years after cessation of consumption, and at least 20 years after cessation, the risk of HNCs may become close to or similar to that of people who do not consume alcohol at all [24].

Both alcohol and smoking are essential factors in the tumorigenesis of HNCs, so together, these habits manifest amplified synergistic effects, with alcohol solubilizing carcinogens from cigarette smoke and contributing to the permeabilization of cell membranes for carcinogens [26, 27]. Together, smoking and alcohol consumption account for approximately 72% of HNCs [1] (Fig. 1).

Chewing Areca nuts (betel quid)

Areca nuts (betel nuts) are the fruits of the Areca palm (*Areca catechu* L.) and, wrapped in betel leaves (*Piper betle* L.), together with limestone dust, obtained by grinding the shells of marine invertebrates or limestone from quarries, catechu, a resinous extract from the matrix of *Senegalia catechu* (L.f.) P.J.H.Hurter & Mabb trees or *Senegalia polyacantha* (Willd.) Seigler & Ebinger subsp. *polyacantha*, and, commonly outside Papua New Guinea, tobacco powder, are called betel quid and chewed by some ethnic groups in Southeast Asia (Bangladesh, Myanmar, China, Cambodia, India, Indonesia, Laos, Malaysia, Nepal, Pakistan, Papua New Guinea, the Philippines, Singapore, Sri Lanka, Taiwan, Thailand, and Vietnam), but also by some minority communities in Fiji, Kenya, Mauritius, South Africa, Uganda, and Tanzania, for their psychotropic effects, due to the alkaloids in Areca nuts (arecoline, arecaidine, guvacine, guvacoline, and arecolidine) [15, 22, 28, 29]. Worldwide, the number of betel quid consumers is 600 million [30, 31]. In ripe Areca nuts, alkaloids constitute a minor fraction (0.15–0.67%), and of these, arecoline is predominant (0.12–0.24%), with the remainder consisting of saccharides (17.8–25.7%), polyphenols/tannins (11.1–17.8%), fats (1.3–17%), fiber (11.4–15.4%), fat (9.5–15.1%), protein (6.2–7.5%) ash (1.1–1.5%) and moisture (38.9–56.7%) [32]. Arecoline has a structure

close to nicotine's [30]. In rats, the metabolization of areca nuts alkaloids in the presence of nitrites results in four nitrosamines (N-nitrosoguvacoline, 3-(methylnitrosamino) propionitrile, 3-(methylnitrosamino)propionaldehyde and N-nitrosoguvacine), two of which (N-nitrosoguvacoline and N-nitrosoguvacine), which have been identified in the saliva of betel quid chewers [33, 34]. Metabolites of alkaloids in Areca nuts are cytotoxic, genotoxic, and carcinogenic through ROS production, DNA damaging, and promoting of inflammation and hypoxia [35, 36], producing oral precancerous lesions and representing essential risk factors in the etiology of oral cancers in people who chew them, particularly in Papua New Guinea. In people who also add tobacco powder to betel quid, smoke, or consume alcohol, their effects are amplified [37].

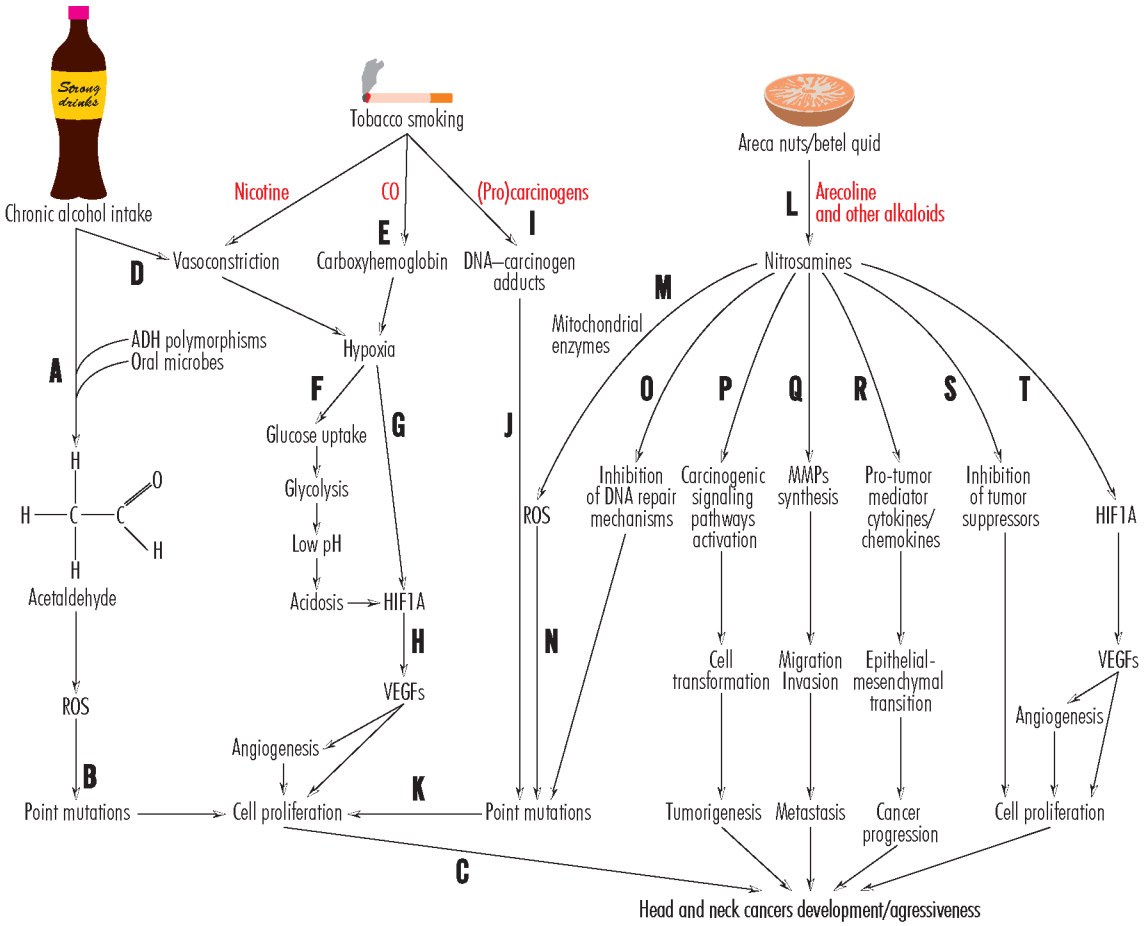

Figure 1. Overview of the mode in which carcinogens derived from alcohol, cigarette smoke and Areca nuts/betel quid lead to HNCs. In the case of alcohol consumption, oral microorganisms, in the presence of ADH polymorphisms, produce acetaldehyde (A), which, *via* ROS produced, can generate point mutations (B), cell proliferation and HNC (C). On the other hand, through vasoconstriction (D), alcohol consumption and nicotine derived from cigarette smoke favor the onset or progression of hypoxia. The most intense hypoxic effect, however, is caused by carbon monoxide (CO), resulting from the incomplete combustion of organic matter in the cigarette (E). It combines with hemoglobin from carbohemoglobin or oxyhemoglobin to form carboxyhemoglobin, a stable complex that can only be broken down by large amounts of oxygen in the blood, reaching through strong ventilation. Hypoxia contributes to the establishment of acidosis (F) and induces HIF1A synthesis (G), which in turn induces the synthesis of VEGFs (H). These lead to angiogenesis and tumour vascularization, and cell proliferation, sustaining the aggressiveness of HNCs (C). Finally, procarcinogens from cigarette smoke are metabolized into carcinogens (I), such as benzo[a]pyrene, which, by complexing guanine in DNA, renders it unavailable for cytosine and causes it to pair with adenine, inducing insertion of a point mutation (J). When these mutations occur in certain genes, they can lead to cell proliferation (K) and HNCs (C). Regular consumption of Areca nuts in the form of betel quid introduces the alkaloids the nuts contain into the body. Arecoline is the most abundant alkaloid in Areca nuts and, in the oral cavity, it can be converted to nitrosamines (L). These can be metabolized by microbial enzymes (M), with the production of reactive oxygen species, which can give point mutations (N). Nitrosamines contribute to the inhibition of error repair mechanisms in DNA, favoring the perpetuation of point mutations (O). Nitrosamines also activate the signaling pathways that maintain carcinogenesis (P), induce synthesis of MMPs (Q), cytokines or chemokines mediating the tumour process (R), inhibit tumour suppressors (S) and promote HIF1A production (T), all of which favor the development and aggressiveness of HNCs.

Carcinogenic and pro-tumor effects of Areca nut extract or arecoline are due: (1) formation of reactive oxygen species by mitochondrial enzymes, species that interact with DNA, proteins and lipids, and produce significant cellular damage [35]; (2) activation of carcinogenic signaling pathways, including RAS–RAF–MEK–ERK [31]; (3) activation of signaling pathways involved in G1/S or G2/M cell arrest [38]; (4) stimulation of synthesis of pro-tumor mediator cytokines/chemokines (IL6, IL8 [39] and receptors EGFR [31]); (5) triggering genetic defects, including hyperdiploid chromosomal changes associated with impaired p53 function and inhibition of DNA repair mechanisms (in keratinocytes and oral epithelial cells) (Shih et al., 2020); (6) inhibition of tumor suppressors, through activation of PI3/AKT, MEK/ERK, AMPK/mTOR, or HIF1A signaling pathways [31]; (7) stimulation of hypoxia-inducible factor 1 (HIF1) production, which contributes to malignant transformation [40]; (8) promotion of cell motility by promoting synthesis of matrix metalloproteinases (MMPs), including MMP, MMP2 [35], MMP8 [41], and MMP9 [42], and suppression of TIMP functions [31], and epithelial–mesenchymal transition [35, 43] (Fig. 1). MMP1 [16, 44] and MMP9 [42] are found at high levels in saliva and tumor tissues of betel quid chewers; MMP1 is proposed to be used as a marker for oral cancer [16, 44].

Several eating habits

It is well known that a balanced diet, including all nutrients from vegetables, dairy, low-fat cheeses, pulses, boiled lean white meat, cooked fish, etc., promotes a healthy lifestyle and reduces the risk of many diseases, including cancers. On the other hand, the predominant consumption of pro-inflammatory diets, fried foods, fatty and processed meats and sweets, and the reduced consumption of fresh fruit and vegetables are risk factors for developing diseases, including laryngeal cancer [45, 46]. Dried and salted meats, including fish, concentrate N-nitrosodimethylamine and N-nitrosoethylamine, which, combined with alcohol consumption, amplify carcinogenic genomic DNA alkylation several-fold in tissues of the oral cavity, pharynx, and larynx [47, 48]. Similarly, the consumption of meat and fried potatoes or eggs, especially when this habit is frequent and is associated with smoking and the consumption of alcohol, seems to favor the development of laryngeal cancers, particularly supraglottic cancers, with odds ratios for the highest level of consumption compared to the lowest of 3.06 for fish or shellfish meat, 1.86 for potatoes, 1.85 for eggs or omelet and 1.63 for beef or veal [49-51]. Some studies [51] indicate a positive correlation between oral cancers and red or processed meat consumption but not between these and oropharyngeal and laryngeal cancers, just as no correlation can be made between fish meat consumption and HNCs. For fried, roasted, or smoked foods of animal origin, thermal preparation favors, under conditions of dehydration, the pyrolysis of polypeptides to amino acids and the interaction between amino acids and creatine, forming polycyclic aromatic hydrocarbons, including benzopyrenes and heterocyclic aromatic amines, which, under the action of cytochrome P4501A2 (CYP1A2) and N-acetyltransferase (NAT2), are activated to mutagens and carcinogens for the upper aerodigestive sphere [51, 52], and smoking meat enriches it in compounds derived from burning wood or coal, including aldehydes, phenolic compounds, volatile hydrocarbons, and some volatile metal compounds. Another compound that results during frying, including that of potatoes, is acrylamide, recognized by the IARC in 1994 as a potential human carcinogen [50, 53]. The formation of these compounds appears to be influenced by the food preparation method, with fat frying generating the highest concentrations of acrylamide and polycyclic aromatic hydrocarbons and air frying lower amounts, but not by the method of thawing frozen products [54].

Other factors

Exposure to solar radiation, some occupations, including those in paper and paper products, metal, leather, food and textile industries, where workers are exposed to asbestos, formaldehyde, coal dust, wood dust, grease, oils, including cutting oils, naphthalene, exhaust fumes, other types of pollution, certain sexual practices that predispose to viral infections, such as sexual promiscuity, same-sex sexual relations or early sexual debut, membership of socially disadvantaged groups, etc., are additional risk factors in the etiology of head and neck cancers [6, 8, 55-58].

Conclusions

HNCs are favored by some lifestyle peculiarities, including heavy smoking (active and passive), alcohol consumption, betel quid (Areca nut) chewing, poor oral hygiene with an imbalance of the local microbial community, -inflammatory diet (e.g., consumption of fried, smoked, or roasted meat), inhalation of chemical compounds, asbestos dust, genetic factors, and HPV and EBV infections. Due to diagnosis at advanced stages, most HNCs often have poor prognoses, low overall response rates, survival of several months without tumor progression, and overall survival of five years or less. Under these circumstances, strategies to prevent HNCs are compulsory and aim at (1) developing efficient algorithms for the early detection of neoplasms in high-risk individuals and reducing contact

with risk factors, including limiting smoking and alcohol consumption, Areca nuts chewing and pro-inflammatory foods consumption; (2) identification of individuals at high risk of developing HNCs, reduction of exposure to airborne pollutants and modification of dietary habits to reduce exposure to orally introduced carcinogens), and (3) halting or slowing the cancer progression, this requiring strict adherence to therapeutic management in these individuals. The data shown here underline the necessity of preventive strategies, including improved algorithms for reducing contact with risk factors and the early detection of HNC in high-risk individuals, as well as for halting or slowing the HCN progression by strict adherence to therapeutic protocols.

Conflict of interest

The authors declare that they have no conflicts of interest.

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