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The influence of dietary & habitual agents in oral carcinogenesis: Short review

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Abstract

The article narrates the influence of day to day dietary as well as habitual agents in carcinogenesis of oral cavity & associated structures. In the modern world, majority of the food consumables are adulterated & availability of such noxious agents for extravagantly sensual satisfaction are easy to reach oral & oropharyngeal carcinomas are becoming increasingly predominant. The article discuss role of each such agent in oral environment & its possible consequences.

Keywords: Food adulterants & oral cancers, food preservatives & oral malignancies, diet habits & oropharyngeal carcinomas, nutritional status, oral habits & cancers

Introduction

This is a coherent review discussing the roles of various habitual and dietary agents in the initiation of oral & oropharyngeal carcinomas, based on articles from 1975 to 2014. The article highlights the limitation of modern world in choosing hazard free consumables. During its journey from the field to the plates, approximately 12,000 adulterants are added unintentionally to food consumables; with purposeful incorporation of >2,500 chemicals to make it more attractive, palatable and to improve the shelf life One such example is the unavoidable intrusion of well known carcinogens - vinyl chloride and acrylonitrile into packed food items, when hot food is packed in plastic wraps; for the reason they are not coming under class of addictive, there is no restriction placed for its incorporation [1].

Various studies from India suggest that the number of HNC can drift from 1,22,643/53,148 to 1,53,636/64,785 cases by 2020 in male/female population, irrespective of its geographical location [2], due to the drastic change in nutritional habits with unhealthy life style practices [4], followed in the last 20 years [4]. From 2010-2020, cancer studies in India projects an expectation of raise in oropharyngeal lesions with proportion of 29.5%, 17.4% & 15.5% in carcinoma mouth, tongue and larynx respectively, contributing to an overall raise (unnoticeable areas, absence of pain and late diagnosis) in total cancer cases [5]. 15% of oropharyngeal carcinomas & 35-50% carcinomas of other parts of body [6] are contributed directly by what we consume [7, 8].

The Structural permeability barrier of Oral Epithelium & other defense mechanisms

The phenomenon of semi permeability in oral mucosa has its regional variations due to the complexity in structural variation of ceramides & cholesterol molecules [9] in different regions; (most permeable non keratinized areas 60%) [10]; making it prone to the various environmental threats [11, 12], with the second permeability barrier - the basement membrane and third a protective melanocyte [13] rich basal layer. Cell Kinetics shows that all these barriers operates a simple diffusion mechanism with maximum permeability in lateral border of tongue and floor of mouth. Higher the permeability potential, more be the chances of developing OSCC [14]. Unlike other tissue lining in gastrointestinal tract, the oral mucosal cells are found to be having biotransformation capacity to metabolize various chemicals intracellular with the help of cytochrome p450 family of enzymes [15].

Intracellular and interstitial fluid antioxidants has a neutralizing action on highly reactive oxygen and nitrogen species, which are a known threat to the lipid and protein structures causing potentially malignant disorders and later OSCC [16, 17]. The sources of reactive oxygen species are carbonated drinks, alcoholic beverages, dental restorative materials and other volatile materials that are taken into the oral cavity [18].

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Studies done on animal models support the anticancer effect of salivary antioxidant mechanisms^[19] which includes various enzymes & molecules like uric acid^[20] (70%) and peroxidases, which are water soluble. Further studies using the Ames test, it is observed that salivary antioxidants are found to have a blocking action on the mutation inducers like 4-nitrosoquinolone-1-oxide^[21].

Classification of various dietary carcinogens

I. Chemical carcinogens

Direct carcinogens (25%) & indirect carcinogens (75%)

II. Dietary & nutritional factors: a)^[23] Micro components/Genotoxic agents;
b) Macro components/Promoting agents.

III. Naturally occurring chemical substances in food supply^[24]

a) Constitutive b) Derived c) Acquired d) Pass-through e) Added naturally.

IV. Exogenous & endogenous agents: [Camargo *et al.* 1999, Gutiérrez, Salsamendi 2001]^[25]

a) Exogenous group - Nutritional habits -food preparation & preservation
- Chemical compounds -Natural & synthetic compounds;
b) Endogenous group- Imbalances related to genetic, endocrine, physiological immunological issues.

V. Genotoxic carcinogens: [Bolt *et al.*; 2004]^[25]

a) Those that react at chromosomal level.
b) Those that react with DNA- 1.initiators 2.borderline 3.weak genotoxic

VI. International agency for research on cancer 2012^[27, 28]

- Group 1:** Carcinogenic eg alcohol, benzopyrene, (S)-NNN, aflatoxin, processed meat, arsenic
- Group 2A:** Probably carcinogenic eg acetaldehyde, nitrosamines, nitrates, nitrites, red meat, mate
- Group 2B:** Possibly carcinogenic eg PAH, quinoline, 2,4-D
- Group 3:** Not classifiable as to its carcinogenicity to humans eg calcium carbide
- Group 4:** Probably not carcinogenic.

I. Influence of habitual agents on oral carcinogenesis:

Alcohol

Acetaldehyde^[27], the highly toxic, mutagenic, carcinogenic ally active metabolite of alcohol is formed either by oral bacterial metabolism or by the action of alleles of alcohol dehydrogenase type-III enzyme ie- type 01 & 02 in various racial and ethnic groups. In those individuals with former allele, there will be faster metabolism of alcohol and more acetaldehyde formation, whereas in the later type, the metabolism will be at a slower rate. This explains the variation in incidence of oral cancers amongst alcoholics^[28]. If the intake exceeds 45ml/day, the risk increases since there will be accumulation of acetaldehyde in oral epithelial cells and salivary gland tissue. Additional damage is ascribed mostly to the action of free radicals and fatty acid ethyl esters^[28]. Whisky and brandy consumption have still higher rate of association with oral cancer due to its increase in ethanol content^[26]. Histopathologically, alcohol induced damage includes nuclear hypertrophy, epithelial atrophy due to reduction in size of cells in stratum germinativum and

dysplastic features with Keratosis^[30]. Researchers found that there will be fat accumulation in salivary gland tissue, acinar swelling and later destruction. Loss of weight and loss of protein content is also observed in parotid gland^[31].

Contaminants in alcoholic beverages Nitrosamines

(Intake shouldn't be more than 1 µg /person)^[32] are alkylating agents that are mutagens, which gets incorporated into the beverages while malt is subjected to direct frying process. These chemicals are first found out in 1978 in German beers, with high concentration up to 68 µg/L. In the later years, the production process was changed to indirect firing of the kiln, temperatures were reduced and in some cases sulfur was introduced to release sulfur dioxide that scavenges oxides of nitrogen that can make amines^[33].

Polycyclic aromatic hydrocarbons

Is from the caramel or from the smoke released during the process of drying germinated barley stored in wooden barrels, from months to years. The heat treatment of wooden barrels^[34] causes toasting of tree raw material and aromatic hydrocarbons are released. Studies show that the concentration of this chemical vary from 0 -172ng L in various preparations, with more carcinogenic potential associated with P.A.H. of higher molecular mass. Varying amounts of carcinogen benzopyrene is also found^[35].

Tobacco chewing

Exposure to tobacco causes chemical inactivation of iron, cyanocobalamin and folic acid in local tissues^[36], irrespective of its systemic status leading to mucosal atrophy and compromised mucosal integrity. The air cured black variant of tobacco is the highly carcinogenic form than flue-cured blond variant, due to its high content of (S)-NNN in smoke; has more hemoglobin adducts and increased urine mutagenicity^[29].

Alcohol tobacco synergism effect

Ethanol can dissolve the lipid barrier of OM, resulting in formation of clefts between cells, making it exposed to chemical carcinogens in tobacco making the risk factor thirteen times more than with tobacco alone. In addition, alcohol increases secretion of more viscous saliva, which don't have any cleansing action, making the carcinogens more durable in mouth, facilitating more penetration. The effect is more prevalent in floor of oral cavity and areas of continuation rather than in buccal mucosa^[37].

Areca nut chewing

Chewing releases nitrosamines^[73] tannins, polyphenols, safrole, hydroxychavicol and catechins^[38] from areca nut that are strongly associated with oral & OPC, with or without the use of tobacco^[39]. The IARC. strongly suggested areca nut^[40] as a carcinogen by pointing out the characteristic oral mucosal lesions associated with the prolonged use of it such as betel chewer's mucosa, OSMF and leukoplakia; eventually turning out into OSCC. The cells being attacked are oral fibroblast myofibroblast and keratinocytes^[38].

Aflatoxin

Aflatoxin class B1 is the most mutagenic and carcinogenic toxin produced by fungus *Aspergillus flavus*; a contaminant fungi found in improperly cured tobacco (concentration of 43,53ppb in chewable tobacco, India). In smoking tobacco, the high temperature of combustion can degrade the toxin^[41].

It is a standard mutator of p53 tumor suppressor gene. If mutation occurs in codon 249 in p53, it's then the hallmark of aflatoxin contamination⁴². More studies are needed to prove the possible links of aflatoxin induced O.C.

Marijuana and Khat/quat smoking

OC. cases has been reported in marijuana smokers (tobacco cigarettes partly replaced), even though there exists no direct association. *Catha edulis*; Forsk is a plant cultivated in some of the African countries and in middle east, leaves of which are excessively consumed by these populations. A few cases of oral leukoplakia and OC. are reported, but more studies needed to prove the association between its use and oral carcinogenesis^[43].

II. Influence of dietary components on oral carcinogenesis

The magnitude of dietary carcinogenic threat lies in finding out the carcinogenic compounds present in thousands of food consumables consumed each day. Carcinogens present in food along with additives is found to have a *direct effect*; whereas *dietary habits has indirect control* over the cellular metabolism. These effects together have an impact on hormonal and metabolic responses to the *milieu interior* of body^[44, 45, 46].

Pubmed data shows meta-analysis demonstrating significance of consuming nitrite processed meat and its association with oropharyngeal carcinomas (91%) in south Americans^[47, 48]. Nitrite cured meat, when used with alcohol beverages, doubles the threat for OSCC risks in South Indians^[49]. Those who consume more cereals and grains are found to be comparatively safer from oropharyngeal cancers, due to reduction in overall dietary fat and calorie intake^[50]. Major observations made in 1970's states that a diet rich in fat, protein and sugar, typically lacking micronutrients (folic acid and cyanocobalamines)^[36]. Is an ideal carcinogenic diet. These type of food habit is observed in 30% of the Western population and in 20% of developing countries. 60% of oral, pharyngeal and esophageal cancers in developing Nations is due to insufficient intake of micronutrients from diet^[51].

Processed meat

Processing of meat produces varying amounts of mutagens, in addition to its rich concentrations of heme iron and saturated fats. When exposed to direct flame, N-Nitroso compounds, P.A.H. and heterocyclic amines are also produced. Meta-analysis on observational studies on meat consumption & OPC. by Jining medical university, China reports heavy consumption of processed meat was found to be having a relation with development of oral & O.P.C. in South Americans. Variations in genetic background, environmental determinants and life pattern are also dependent factors^[47].

Nitrates and nitrites

Reports on carcinogenic effects of nitrosamines from nitroso compounds dates back to editions of Nature in seventies. Due to its unique property of imparting eye catching colour, attractive flavor and texture to processed meat, in addition to its antimicrobial action, fixation and control over lipid oxidation; neglecting the joined reports of WHO & I.A.R.C. 2006, still these salt are widely in use. Oral microflora such as *Streptococcus salivarius*, *S. mitis* & *S. boves*, under hypoxic conditions secretes bacterial nitrate reductase enzymes, which favors nitrate reductive process producing NO in gingival sulcus and posterior surface of tongue (70%). Some of the nitrites gets transformed into NO₂ & N₂O₃, which causes

tyrosine nitration, leads to further more unfavorable conditions. Those which reaches stomach or intestine, gets absorbed and are excreted through saliva (25%) by anion transport mechanism. This is the reason why the nitrate concentration is 10-20 times more in saliva than in plasma. These nitrites & various amine precursors in oral cavity are found to have an effect on the etiology of oral carcinogenesis. High concentrations of salivary nitrates & nitrites in OSCC & OSMF patients confirms the role of these salts as chemical carcinogens^[52, 53, 54].

Polycyclic aromatic hydrocarbons

Methods of traditional preservation of meat and fish includes smoking or salting for future adversity. Currently these items are on the top of menu for its specific flavor and taste. Smoked food contains phenolic compounds and canned fish contains oil as preservatives, which are hazardous, if consumed regularly. Due to its lipophilic nature, P.A.H. like benzopyrene (used as marker for carcinogenic P.A.H.), benzoperylene, fluoranthe, benzofluranthene and benzoanthracene, formed from the process of incomplete combustion of processed meat gets readily absorbed into the cells and induce the change^[55, 56].

Heterocyclic aromatic amines

Maillard reaction/Non-enzymatic browning reaction occurs, when meat is deep fried or grilled. During this reaction, creatine in muscle breaks down, condenses with other amino acids and form various H.A.A. They have a common imidazole ring to which an exocyclic amino group is attached. Thus the name amino-imidazo-azaarenes. There are mainly four anticipated human carcinogenic H.A.A. out of which: MeIQ: 2-Amino-3,4-dimethylimidazo [4,5-f] quinoline is found to be a genotoxic agent causing increased incidence of OSCC in experimental animal studies^[57, 58].

Heme iron

Red meat whether in its processed or raw form, is found have highest concentration of carcinogenic content -heme iron. Tobacco smoking along with intake of heme iron induces several phase 1,2 enzymes in our tissues that in turn induces metabolic activation of enzymes that activates carcinogens in processed meat. Heme iron induced free radical formation is the from combination of oxygen with heme iron can either be due to Haber-Weiss reaction or due to Fenton reaction or both. Fenton reaction is extremely damaging and causes activation of oncogenes, suppression of tumor suppressor genes, DNA strand breakage, peroxidation of lipid & mutagenesis. Due to these reasons, researchers warn the excessive consumption of heme iron rich food in leukoplakia cases with high risk. Heavy intake of alcohol along with red meat consumption is widely found in Kerala, India. Researchers found that NO formed from nitrites reacts with heme and form nitrosyl heme. This reaction is called nitrosylation of heme in myoglobin. Thus formed nitrosyl heme is pink in color and more toxic than heme^[59, 60, 61].

Fat consumption & salivary gland tumorigenesis

Dietary fat intake has a control over the multiplication of salivary gland cells and oral epithelium. Experimental and epidemiological data shows that salivary gland tumor genesis is associated with high consumption of saturated fat (tallow, lard, bacon, sausages). More the intake of fat, there will be an associated deficiency of omega -6-linoleic acid & omega-3-linolenic acid, which in turn leads to hyper proliferative cells

Mate drinking

Metaanalysis and several epidemiological studies reveals the association of repeated oral mucosal injuries associated with consumption of very hot beverage drink infused with *Ilex paraguariensis*, through a metal straw, in Latin America. It is hypothesized any chemical carcinogen present in this beverage can easily pass through the damaged mucosal barrier, which in turn will might be the reason for carcinomatous change [64, 65].

Volatile Chemical carcinogens

A study conducted in Germany, Brazil and Switzerland shows that kitchen workers who are continuously exposed to indoor air contaminated with volatile carcinogens arising from fumes of fossil fuels, for more than 40 years, are found to be having increased incidence of OPC with high mortality rate [43, 66].

Arsenic poisoning & Basal cell carcinoma

Drinking water [59], some of the ayurvedic and Chinese herbal preparations⁶⁷, ceramic coated with enamel and insecticides⁶⁸ are the present arsenic threats [69]. Under certain conditions, arsenic can act as a tumor promoter, co-carcinogen or progressor [70]. Once the metalloid [71], 30% arsenic (IV) is totally eradicated from the treatment of syphilis, peak in nasopharyngeal carcinomas also reduced.

Agent Orange

About 77 million liters of rainbow herbicides including agent orange (contains 2,4-D) was sprayed in Vietnam by U.S. military during the war, for its defoliating effect on plants. The incidence of salivary gland carcinomas & oral cavity were significantly high in exposed groups even after decades. Under this circumstance, the another threat of genetically modified soya and corn, that is supposed to survive dousing with 2,4-D is waiting for approval in USA, for agricultural use. [62, 65, 69, 72].

Conclusion

Very limited literature available on the influence of dietary preservatives and associated factors in the initiation of various malignancies of oral and oropharyngeal carcinomas. No clinical studies so far have been done from Asia regarding the carcinogenic role of various agents used in the manufacturing and processing of food materials. Articles other than English language were not considered in this review. For concluding, no edible items are totally contamination free. For a healthy life, we should prefer vegetarian diet, preferably farmed one's own or from the local market. Total avoidance of junk food and non vegetarian diet adds up life to your Life.

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