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Review Article

TEA AND ORAL CANCER: A REVIEW

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ABSTRACT

Tea is the most widely consumed beverage worldwide and important agricultural product. It is consumed in different forms namely, oolong, green, and black tea .Being rich in natural antioxidants, tea is used in the management of different types of cancers including oral cavity. The development of oral cancer is a tobacco related multistep process. Micronuclei (MN) act as a biomarker which is related with tobacco-associated genetic mutations. The present review focuses on the tea antioxidants and their mechanism of protective effects on oral cancer.

Keywords: Tea, Cancer, Polyphenols, Micronuclei.

INTRODUCTION

Oral cancer is the sixth most common human cancer[1], representing 3% of all types of cancer. They are located in the oral cavity in 48% of cases, and 90% of these are oral squamous cell carcinoma[2]. They are sometimes preceded by precancerous lesions, such as leukoplakia and erythroplakia. More than 300,000 new cases of oral squamous cell carcinoma are diagnosed annually [3]. The most common site for intraoral carcinoma is the tongue, which accounts for around 40% of all cases in the oral cavity proper. Tongue cancers most frequently occur on the posterior-lateral border and ventral surfaces of the tongue. The floor of the mouth is the second most common intraoral location. Less common sites include the gingival, buccal mucosa, labial mucosa, and hard plate. The incidence of oral cancer has significant local variation. Oral and pharyngeal carcinomas account for up to half of all malignancies in India and other Asian countries, and this particularly high prevalence is attributed to the influence of carcinogens and region-specific epidemiological factors, especially tobacco and chewing betel quid.

Risk Factors of Oral Cancer

The most important risk factor for the development of oral cancer in the Western countries is the consumption of tobacco[4] and alcohol[5]. Although drinking and smoking are independent risk factors, they have a synergistic effect and greatly increase the risk together. The use of smokeless tobacco products such as gutkha and betel quid in Asian countries[6,7].

GENETIC: Several studies have reported a significant familial component in the development of oral cancer. Familial aggregation of oral cancer, possibly with an autosomal dominant mode of inheritance, is observed in a very small percentage of oral cancer patients[8]. Polymorphic variation of genes in the xenobiotic metabolism pathways such as in CYP family or the genes coding for glutathione S-transferase-M1[9,10] and N-acetyltransferase-2 may be implicated[11]. Individuals that carry the fast-metabolizing alcohol dehydrogenase type 3 (ADH3) allele[12]may be particularly vulnerable to the effects of chronic alcohol consumption and could be at increased risk to develop oral cancer[13]. The single nucleotide polymorphism A/G870 in the CCND1 gene that encodes Cyclin D is associated with susceptibility to oral cancer.

INFLAMMATION: Cytokines, including interleukins (ILs), tumor necrosis factors (TNFs), and certain growth factors are an important group of proteins that regulate and mediate inflammation and angiogenesis. Genetic association studies suggest a putative correlation between functional DNA polymorphisms in cytokine genes and oral cancer [14]. Increased serum levels of proinflammatory cytokines, interleukin (IL)-1β, IL-6, IL-8, and TNF-α as well as the anti-inflammatory cytokine, IL-10, are seen in patients with oral cancer.

INFECTION: Human papillomavirus (HPV), particularly HPV type 16, may be an etiologic factor, especially among persons who do not smoke or drink alcohol [15,16]. Tumor HPV status is a strong and independent prognostic factor for

survival among patients with oropharyngeal cancer[17]. The mouth contains a variety of different surfaces that are home to a huge diversity of micro-organisms, including more than 750 distinct taxa of bacteria, thus suggesting that the oral squamous epithelium is constantly exposed to a variety of microbial challenges, on both cellular & molecular levels[18,19].

TOBACCO: Nicotine stomatitis is a thickened, hyperkeratotic alteration of the palatal mucosa that is most frequently related to pipe smoking, but milder examples can also develop secondary to cigar smoking or, rarely, from cigarette smoking (Warnakulasuriya et al., 2007). Another specific tobacco-related oral mucosal alteration occurs in association with smokeless tobacco use, such as either snuff or chewing tobacco (Neville and Day, 2002).Such lesions typically occur in the buccal or labial vestibule where the tobacco is held, but they can also extend onto the adjacent gingival and buccal mucosa. Early lesions show slight wrinkling that disappears when the tissues are stretched. Other lesions may appear as hyperkeratotic, granular patches. Advanced lesions exhibit greatly thickened zones of grayish white mucosa with well-developed folds and fissures[21].

MUTATIONS: Genetic mutations often produce early phenotypic changes that may present as clinically apparent, recognizable lesions. An oral premalignant lesion is an area of morphologically or genetically altered tissue that is more likely than normal tissue to develop cancer. The reported rates of malignant transformation of leukoplakia range from less than 1% to 18% [22,23]. A velvety reddish mucosal lesion, known as erythroplakia, is associated with a higher rate of cancer development, occurs much less frequently, and is more difficult to detect clinically than oral leukoplakia. Virtually all erythroplakic lesions contain severe dysplasia, carcinoma in situ, or early invasive carcinoma at the time of presentation [24]. Formalized classification and staging systems for oral preneoplastic lesions have been proposed[25,26].

PRENEOPLASIA: There are clinically apparent oral premalignant lesions of oral cancer. They include leukoplakia, erythroplakia, nicotine stomatitis and tobacco pouch keratosis, lichen planus, and submucous fibrosis[27].

LEUKOPLAKIA: The term "leukoplakia" is a white lesion of the tongue that probably represented a syphilitic glossitis [28]. Leukoplakia is seen most frequently in middle aged and older males, with an increasing prevalence with age. Fewer than 1% of males below the age of 30 have leukoplakia, but the prevalence increases to an alarming 8% in men over the age of 70 [29].The prevalence in females past the age of 70 is approximately 2%. The most common sites are the buccal mucosa, alveolar mucosa, and lower lip.

ERYTHROPLAKIA: The term "erythroplasia" originally used by (Queyrat, 1911) to describe a red, precancerous lesion of the penis is used for a clinically and histopathologically similar process that occurs on the oral mucosa[30]. Oral erythroplakia occurs most frequently in older males and appears as a red macule or plaque with a soft, velvety texture. The floor of mouth, lateral tongue, retro molar pad and soft palate are the most common sites of involvement.Often the lesion is well demarcated, but some examples may gradually blend into the surrounding mucosa. Some lesions may be intermixed with white areas (erythroleukoplakia). Erythroplakia is often asymptomatic, although some patients may complain of a sore, burning sensation.

Beneficial Effect of Tea

Tea, other natural dietary agents have drawn substantial attention from both researchers and the general public because of their ready availability, low toxicity, and potential ability to suppress carcinogenesis and reduce the risk of cancer [31].Tea beverage is an infusion of the dried leaves of Camellia sinesis, a member of Theaceae family. It is an evergreen shrub or tree that can grow to a height of 30 feet, but is usually clipped to a height of 2.5 feet in cultivation. The tree or shrub is heavily branched with dark-green, hairy, oblong, ovate leaves cultivated and preferentially picked as young shoots. Older leaves are considered to be inferior in quality. Freshly harvested tea leaf is processed differently in different parts of the world to give oolong tea (2%), green tea (20%) or black tea (78%) [32].

TYPES

GREEN TEA: Green teas are not fully fermented like black teas, or partially fermented as oolongs. Instead, the tea leaves are plucked, steamed or pan fried, (which removes the fermentation enzymes), rolled, and then dried. This process yields a chemical composition in green tea similar to the fresh tea leaf. Green teas are generally produced in two different varieties, white tea and yellow tea, the latter being less fermented because of a process known as wilting. Green tea has a high content of vitamins and minerals including ascorbic acid (vitamin C), which is present in amounts comparable to a lemon and several B vitamins, which are water-soluble and quickly released into a cup of tea. Green tea polyphenols may account for up to 30% of the dry weight [33]. Most of the green tea polyphenols are flavonols, commonly known as catechins. Some major green tea catechins are (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG), (-)-epicatechin (EC). (+)- gallocatechin, and (+)-catechin [34].The green tea catechins have been shown to be more effective antioxidants than Vitamins C and E [35], and their order of effectiveness as radical scavengers is ECG>EGCG>EGC>EC>catechin. The metal-chelating properties of green tea catechins are also important contributors to their anti oxidative activity[36,37,38].

BLACK TEA: In the process of manufacturing the black tea, the harvested leaves are allowed to wither. Known as 'withering', this process softens up the tea leaves. Next the leaves are rolled (crushed). After the leaves have been crushed, they often bunch together in balls and must be unrolled so as to allow the entire surface of leaf to be exposed to air for an even fermentation. During the manufacture of black tea, the monomeric flavan-3-ols undergo polyphenol oxidase-dependent oxidative polymerization leading to the formation of bisflavanols, theaflavins, thearubigins, and other oligomers in a process commonly known as "oxidation".Theaflavins (about 1%-2% of the total dry matter of black tea), including theaflavin, theaflavin-3-O-gallate, theaflavin-3'-O-gallate, and theaflavin-3, 3'-O-digallate, possess benzotropolone rings with dihydroxy or trihydroxy substitution systems, which give the characteristic color and taste of black tea. About 10%- 20% of the dry weight of black

tea is due to thearubigins, which are more extensively oxidized and polymerized.

OOLONG TEA: Being an intermediate between black and green tea – oolong tea is partially fermented. The leaves are partially withered, then allowed to ferment immediately. The leaves are then fired, rolled, and then allowed to partially ferment again. The fermentation process results in the oxidation of simple polyphenols, giving oolong tea its characteristic color and flavours[39]. Oolong tea, a partially oxidized tea, contains monomeric catechins, theaflavins, and thearubigins along with some characteristic components, like epigallocatechin esters, theasinensins, dimeric catechins and dimeric proanthocyanidins. The flavanols are easily oxidized to the corresponding O-quinones.

EFFECT OF TEA ON ORAL CANCER

Cancer in the oral cavity is associated with cigarette smoking and tobacco use[40]. A series of studies in animal models, especially in mice and rats, employing the appropriate carcinogens, mainly nitrosamine and in particular 4-(methylnitrosoamino)-1-(3-pyridyl)-butanone (NNK) found in tobacco have revealed that green and black tea or the corresponding polyphenols decrease the incidence of these cancers through inhibition of oxidative reaction caused by the carcinogens[41, 42]. Formation of nitrosamines, the carcinogens also found in tobacco,can be prevented by phenolics of green tea[43]. Green tea polyphenols may be chemopreventive or inhibitory towards oral leukoplakia[44]. Both green and black tea, are a natural source of fluoride and an effective vehicle for fluoride delivery to the oral cavity. After cleansing the mouth with tea, approximately 34% of the fluoride is retained and shows a strong binding ability to interact with the oral tissues and their surface integuments[45]. This fluoride content may have a beneficial impact on caries and may carry out a wide range of biological activities including prevention of tooth loss and oral cancer[46,47]. EGCG treatment inhibits the phosphorylation of EGFR and its downstream targets AKT and ERK and potentiates the effects of the EGFR tyrosine kinase inhibitor erlotinib in head and neck cancer[48]. Tsao et al. have conducted an important phase II randomized, placebo controlled trial of green tea extract (GTE) in patients with high-risk oral premalignant lesions. Hong et al. conducted the first randomized clinical retinoid trial, which showed that high-dose 13-cisretinoic acid (13-cRA) significantly reduced the size of oral premalignant lesions and reversed dysplasia [49]. The combination of high-dose 13-cRA, α-IFN, and α-tocopherol seemed to be very effective in delaying head and neck–associated second primary tumors and recurrence[50].

Micronuclei: A cancer biomarker

Micronuclei are extra nuclear cytoplasmic bodies. It has been reported as marker for high cancer risk as they arise in response to carcinogens. The formation of micronuclei can be induced by substances that cause chromosome breakage (clastogens) as well as by agents (aneugens) that affects the spindle apparatus[51]. The frequency of micronucleated exfoliated cell elevates in human tissues, which appear to be the main targets of carcinogens and from which the carcinomas arise[52]. Micronuclei are induced in oral exfoliated cell by a variety of carcinogenic substances which is found in tobacco ,betel nut and alcohol[53]. It has been reported that potent clastogenic and mutagenic effects which are produced by tobacco specific nitrosamines, are responsible for the induction of chromatid / chromosomal aberrations resulting in the production of micronuclei[54].

Criteria for identifying micronuclei as given by Heddle & Countryman (1976) are:

1. Diameter less than 1/3rd the main nucleus.
2. Non-refractility (to exclude small stain particles).
3. Colour same as or lighter than the nucleus (to exclude large stain particles).
4. Location within 3 or 4 nuclear diameters of a nucleus; and not touching the nucleus (to make frequency measurements meaningful).
5. No more than 2 micronuclei associated with one nucleus[55].

Administration of black tea to subjects with oral leukoplakia resulted in a gradual reversal of the leukoplakia both on clinical observation and at cellular level as assessed by MN and chromosomal studies [56].Both the black tea and green tea extract decreased MN rates . The decrease in the MN indicated that the black tea and green tea were not genotoxic and clastogenic agents. The antigenotoxic and anticlastogenic properties of the teas might be due to the catechins (polyphenols) present in the tea. Many studies have demonstrated that tea catechins could suppress the genotoxic activity of various carcinogens with both in vitro and in vivo systems[57,58,59]. It have shown that there is minimal genotoxic concern with a decaffeinated green tea catechin mixture. The antigenotoxic and anticlastogenic activities of the tea are mostly due to its antioxidant activity that inactivates the direct carcinogens[60]. The antioxidant property has been highly attributed to the polyphenolic compounds in the tea. Catechins and flavonoids from the polyphenols are primarily responsible for the beneficial healthful properties of the tea[61,62].

CONCLUSION

Oral cancer is the sixth largest group of malignancies worldwide. The process of formation of oral cancer results from multiple sites of premalignant changes in the oral cavity. Micronuclei act as a biomarker of squamous cell carcinoma. Percentage of MN formation has been observed in pre cancerous lesions of the oral cavity of betel quid chewers.The polyphenols present in tea decrease the risk factor of specific type of cancers by inducing phase I and phase II metabolic enzymes that increase the formation of carcinogens. We have screened 311 subjects from different areas of Eastern, North Eastern India and also from RKMSP Hospital, Kolkata. Out of which 61.09% had betel quid chewing habit. Percentage of micronuclei is higher than the normal in cases who had betel quid chewing habit and after supplementation of tea micronuclei percentage are lower than before. Overall tea is an affordable beverage of natural origin, shown some protective effect and also reducing the risk of cancer."

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