REVIEW ARTICLE

Cancer Development under Tobacco, Alcohol, and Opportunistic Microbiota Action and its Reduction with Oleuropein

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ABSTRACT

Oral cancer is the sixth widespread malignancy in the world and one of the leading causes of death. Tobacco and alcohol consumption appears to be the major factors causing oral cancer because many studies report its prevalence resulting from such habits as smoking and alcohol consumption. This article provides an overview of the various etiological agents and risk factors that cause the development of oral cancer and proposes the derivative from olive to obtain the therapeutic effect in cancer treatment.

Key words: Alcohol, microbiota, oleuropein, oral cancer, risk factors, tobacco

INTRODUCTION

A large number of studies have shown that oral cancer is one of the malignancies that constitute a major health problem and is one of the leading causes of death. Potentially oncogenic bacteria in the oral cavity also may lead to cancer, ergo knowing their action during human cell carcinogenesis, we may suggest possible ways to reduce cancer.

It is well known that a cancer is the second main cause of death in the world, and oral cancer is the sixth widespread common malignancy. First of all, oral cancer is prevalent in patients with habits of smoking and alcohol consumption.[1,2] The recent global assessments of cancers attributable to infection, obesity, and ultraviolet radiation have shown the variability in their importance for different parts of the world. Ergo, we need to tailor cancer control actions in accordance with localization and limited patterns of risk factors as well. Among men, the most common types of cancers are lung, prostate, colorectal, and stomach cancers, while among women, the most common are breast, colorectal, lung, and cervix cancers, and the most commonly diagnosed in both sexes cancer is a lung cancer (11.6% of the total cancer cases).[1] This is the leading cause of cancer death because it counts for about 18.4% of the total cancer deaths, followed by female breast cancer (11.6%), a little less – by prostate (7.1%), and colorectal cancer (6.1%).[3] Colorectal cancer can result from cancer of the oral cavity.[2] Oral squamous cell carcinomas (OSCCs) are accepted as the main etiological factor resulting from tobacco and alcohol use. Prevention of oral cancer requires healthy life-style, minimizing risk factors of tumor, and early diagnosis.[4] One of the main factors which influence most diseases is a genetic factor (genetic predisposition). Development of oral or other types of squamous cell carcinoma is influenced by this factor plus tobacco, alcohol, diet and nutrition, viruses, radiation, ethnicity, familial and oral thrush, immunosuppression, use of mouthwash, syphilis, dental factors, and occupational risks.[5] Ram *et al*. along with Malay *et al*. report that in Asia and India, tobacco and alcohol consumption is thought to be the major determinants of oral cancer and informs that its prevalence is due to smoking and alcohol consumption in this region.[5,6] The American Cancer Society estimates that there were approximately 42,440 cancers of the oral cavity and pharynx in the U.S., leading to 8390 deaths in 2014. In the

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United States, the major risk factors for oral cancers are also the use of tobacco and alcohol; they account for approximately 75 up to 80% of all oral cancer causes. Tobacco smoking and alcohol are known as the main etiological factors in OSCC. Tobacco comprises many carcinogens, including polycyclic hydrocarbons and nitrosamines. A direct proportional effect has been found between the amount of tobacco used and the risk of OSCC. This risk can be reduced by quitting tobacco smoking, but there is not a fully guarantee to avoid cancer (30% in the first 9 years and 50% for those over 9 years).[7] Cessation of smoking can be associated only with reduced risk of this cancer. The risks varied by type of cigarettes smoked: The risk is lower among consuming filtered cigarettes only, but high enough among consuming non-filter or mixed cigarettes. Research in Poland also disclosed that smoking accounted for 57% of oral cancer cases, alcohol for 31%, and low fruit intake – for 12% of total oral cancer cases. Risks for the low frequency of tooth brushing and dental check-ups were accepted in Poland as 56% and 47%, respectively.[8]

The International Agency for Research on Cancer Monograph 44 on alcohol and cancer in 1988 has also reported that alcohol consumption is strongly associated with an elevated risk of oral and pharyngeal cancers.[2] The risk is nearly 3.2–9.2 for more than 60 g/day usage of alcohol, that is, in more than four drinks in a day. Thereby, cancer risk increases with the intensity of alcohol use. No obvious association is observed for the duration of alcohol use, but the decrease in cancer risk is observed in the case of alcohol cessation. Similar associations have been observed among non-smokers. In general, the more is alcohol consumption in each population; the more is the risk of cancer. Surprisingly, alcohol and tobacco simultaneously, consumption shows the greater than multiplicative synergistic effect. Compared with alcoholics, after alcohol cessation, a decreased risk of cancer for approximately 10–15 years was observed.[2]

In Central Serbia, analysis of mortality from carcinomas localized in the region of the lip, oral cavity, and pharynx generally localized in the hypopharynx shows that there was a statistically significant difference in the number of deaths between men and women in the ages of 40 and over, and the male/female cancer mortality ratio was 4.56:1. However, there was no increase in mortality from these cancers for both genders during the 17-year period.[7] Genden *et al*. have identified that outside of North America, dietary habits, such as chewing betel and areca nuts, raise risks for the development of oral cancer.[9]

In oral and esophageal cancer, lesions and their associated lymph nodes certain common oral bacteria may develop. Studies have reported that the microbiota in OSCC lesions differs from that found in the soft tissues of OSCC-free individuals.[10] Some authors have shown that the following bacteria were found in oral cancer and epithelial precursor lesions areas: *Clostridium, Fusobacterium*, *Haemophilus, Actinomyces*, *Enterobacteriaceae* and *Veillonella*,[11] *Pseudomonas aeruginosa*, and *Pseudomonas maltophilia* that account for 80% of opportunistic infections. By the way, *P. aeruginosa* infection has also been observed in patients with cancer, cystic fibrosis, and burns, and the case of fatality, in this case, is approximately 50%. There are also other infections caused by *Pseudomonas* species, among which endocarditis, pneumonia, and infections of the urinary tract and central nervous system, skin, especially in the areas of eyes and ears, and musculoskeletal system, are mentioned in the literature. *P. aeruginosa*, along with *Capnocytophaga gingivalis*, *Prevotella melaninogenica*, and *Streptococcus mitis*, may be one of the causes facilitating complication of oral cancer.[10] It is known that metabolites play a huge role in tumor development. In addition, nowadays, it becomes clear that carcinogenesis is the result of the influence of the whole community of microbes on the body, but not of a single micro-organism. Moreover, since microflora is the most important source of metabolites in the body, tumorigenesis can be regulated by the effect on body micro-organisms. After all, it is known that the progression of a tumor is closely related to the release into the body of certain produced by pathogens toxins, which are capable to affect the immune system, reducing immune respond, and ensuring the further development of the tumor.[11,12] For example, *Fusobacterium nucleatum* and *Porphyromonas gingivalis* are known to be tumor-triggering micro-organisms. Many works have also shown that these two periopathogenic species, namely, *F. nucleatum* and *P. gingivalis* are essential in the development of colorectal and pancreatic cancer. The scientists suggested three main mechanisms of oral microbiota action on the pathogenesis in cancer. First, the bacteria stimulate chronic inflammation and producing inflammatory mediators facilitate cell proliferation, leading to mutagenesis, which means oncogene activation with further angiogenesis. Second, bacteria affect cell proliferation by the inhibition of cellular apoptosis. Third, bacteria produce substances that already act as carcinogens.[11-13]

Mager *et al*.[10] tested 40 bacterial oral species from a group of cancer-free individuals and from a group of subjects with OSCCs. The authors established that high salivary counts of *C. gingivalis*, *P. melaninogenica*, and *S. mitis* may be diagnostic indicators of OSCC. *C. gingivalis along with Fusobacterium* sp. and *P. gingivalis*, also *Peptostreptococcus* sp. and *Streptococcus* sp. are found to have an impact on cancer development in the gastrointestinal tract. *Helicobacter pylori* is also among the pathogens, which can be accepted as bacterial carcinogens.

It has been suggested that *F. nucleatum* may serve as a complementary micro-organism allowing other oral microbes such as *Porphyromonas* sp., *Peptostreptococcus* sp., and *Parvimonas* sp. to adhere to the tissues of the oral

cavity by adhesion.[12,13] Oral microbes form a joint biofilm that alters the properties of the epithelium and stimulates the development of infiltration and inflammation, which, in turn, leads to cell biotransformation and triggers oncogenesis. As the tumor grows, proteins, and peptides, which are the products of the vital activity of microbes, are released into the medium. The constant presence of the inflammatory process in the body supports the formation of a new biofilm; this lasts until the process passes to the colon, where metabolic products mentioned above cause an oncological process.[12]

The discovery of antibiotics has revolution the treatment of tumor and infectious diseases, but the micro-organisms have evolved and adopted in parallel.[14] By change of own genetic information, the bacteria gained a chance to avoid the therapeutic biocide and have resistance against various antibiotics.[12,13] As has informed the World Health Organization, drug-resistant strains are distributed all around the world, and new resistance mechanisms are spread globally.[12] Infection with these bacteria is even more complicated, and the treatment of such complicated disease is limited; therefore, the medicine needs absolutely new treatment directions with species that can prevent mutagenesis, and among them, the natural phenols are the most widely recognized molecules.[15] Investigations have shown that oleuropein, the main phenolic component of *Olea europaea* L., has several health-beneficial properties, among which one may count it is an antioxidant, anti-inflammatory, cardio- and neuro-protective, and anti-cancer properties.[15,16] Oleuropein from the olive tree is accepted as an immunomodulator, it was assessed *in vitro* and the sepsis caused by *P. aeruginosa*. After the addition of oleuropein to monocyte and neutrophil cultures, malondialdehyde, tumor necrosis factor-alpha, interleukin-6, and bacterial counts were estimated in them, even tissue bacteria decreased in tissues processed with oleuropein. It is considered that oleuropein rises survival in sepsis probably by promoting phagocytosis or maybe inhibiting the biosynthesis of pro-inflammatory cytokines,[17] ergo oleuropein from olive oil may be suggested as one of cancer reducing compounds.

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