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Diet and selected stimulants as factors promoting carcinogenesis in oral cancer

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Abstract

Introduction and purpose

Oral cancer belongs to a heterogeneous group of head and neck cancers. In many cases, it is detected at an advanced stage, which translates into a relatively high mortality rate among patients. For this reason, the identification of risk factors promoting carcinogenesis is of great importance in terms of prevention. The purpose of our study is to demonstrate the relationship between the type of diet consumed and the intake of stimulants and the risk of developing oral cancer.

State of knowledge

This article is an overview of selected dietary ingredients and stimulants - tobacco, alcohol and betel, presenting their possible effects on the oral area. We have presented both dietary products known for their harmfulness and those with health-promoting effects.

Material and method

In our work, we focused on analyzing medical literature available on PubMed and Google Scholar. The sources we have chosen are based on studies conducted in epidemiology, biochemistry and oncology.

Summary

Dietary habits and ingested stimulants have a direct impact on the development of oral cancer. Depending on the content of various components, the diet may exhibit protective properties or promote carcinogenesis. On the other hand, chronic habitual use of certain substances has been found to be a strong factor in increasing the risk of oral malignancies. Therefore, efforts should be made to raise public awareness of the potential consequences of pro-inflammatory diets and stimulants intake.

Keywords: Oral Cancer, Risk factors, Diet, Pro-inflammatory Diet, Polyphenols, Tobacco, Alcohol, Betel

Introduction

Oral cancer is, according to the definition, a malignant neoplasm of the mucous membrane that can involve the area of the front 2/3rds of the tongue, lips, cheeks, floor of the mouth, hard palate, alveolar processes, gingivae, and the retromolar triangle.[1] It remains a serious healthcare problem due to its late detection rate and thus significantly lower five-year survival than when detected in the early, localized stages.[2] Alarming data is coming from India, a country with one of the highest incidences of this disease in the world, where it has been calculated that only about 0.9% of women and 1.2% of men have ever had an oral cancer screening.[3]

The cancer can develop on the basis of pre-existing precancerous lesions, the most common being leukoplakia and erythroplakia.[4]

To date, a number of risk factors for the development of oral cancer have been described, ranging from non-modifiable ones, such as genetic predisposition, to the relatively recently described role of disorders of the oral microbiome, to modifiable factors, such as stimulants used or dietary components.[5]

Purpose

In our study, we summarized the modifiable risk factors for oral cancer known to date related to diet and stimulants used, highlighting tobacco, not only in the form of classic cigarettes, but also smokeless tobacco and e-cigarettes, as well as alcohol and betel, a chewing stimulant popular primarily in South Asian and Southeast Asian countries.

The purpose of our study is to highlight the risk factors for oral cancer that can be reduced or eliminated, which we believe can help reduce the incidence and increase the survival rate of this cancer.

Material and methods

The specific location of oral cancer, which is the oral cavity, encourages to look for risk factors for the formation of malignant lesions in this area among the components supplied directly with food.

Due to the increase in the incidence of oral cancer observed in recent years, we would like to analyze the relationship between the type of diet consumed and the stimulants taken and the risk of developing this cancer.

To this end, our work focused on a review of the databases of medical articles available in PubMed and Google Scholar, focusing mainly on oncology and epidemiology.

Results

In our review, we included basic epidemiological data on oral cancer, its diagnosis and a summary of the risk factors for this condition known to date associated with dietary components and stimulants.

We described the influence of diet, tobacco, alcohol and betel on the process of carcinogenesis, and highlighted the role of precancerous lesions in the process of oral cancer formation.

Epidemiology and mortality

Oral cancer is among the most common malignancies worldwide - according to available sources, it ranks 6th among them.[6] Recent years have seen an upward trend in the number of new cases. It is estimated that the annual number of cases (including throat cancer) is about 400,000, and in Europe alone more than 65,000.[7] Such high patient increases make oral cancer a serious health problem and oncological challenge.

Oral cancer belongs to the group of head and neck cancers, accounting for about 48% of all cancer cases among them. Its predominant form is squamous cell carcinoma (SCC, about 90% of cases).[5] Other malignant lesions of the oral cavity area include lymphomas, sarcomas or tumors originating in the salivary glands, as well as metastases of tumors from other areas.[8]

Survival rates for oral cancer depend on the stage of the tumor and the timing of the introduction of appropriate management. For early diagnosis, the 5-year survival rate is as high as 83.7%. However, it is assumed that up to 70% of patients are diagnosed at a late stage, which significantly reduces the chances of cure. Diagnosis of oral cancer with the presence of distant metastases reduces the value of the above rate to less than 40%.[9]

Diagnosis

In the initial stages which have the best prognosis, oral cancer is usually asymptomatic.[10] Precancerous lesions - leukoplakia, erythroplakia, lichen planus - are an important concern, as it is estimated that up to 50% of oral cancers can form on their basis.[5] Early detection and treatment of these lesions have a positive impact on oral cancer morbidity and mortality.[2] The diagnostic process should consist of a thorough basic physical examination - visual inspection and palpation, which can detect a significant number of cancers. The greatest role is attributed to dentists, who are usually the first health care professionals with the opportunity to thoroughly evaluate the oral cavity; however, the role of self-examination is also important.[5,11] There are reports of a positive impact of oral self-examination education on awareness of potentially premalignant lesions and cancer, which can result in earlier detection of dangerous lesions.[12] The gold standard remains histopathological examination.[5,10]

Diet

Diet is a direct determinant of head and neck cancer risk. One of the main aspects concerning the influence of nutrients on possible carcinogenesis is the inflammatory potential of the diet. Its value is based on the ratio between products that increase inflammation and those that neutralize it.[13]

A pro-inflammatory diet is characterized by the intake of substances that contribute to and maintain inflammation in the body. Their consumption predisposes to the synthesis of biomarkers - including IL-6, IL-8, IL-10, CRP, TNF-alpha.[13] Elevated levels of interleukins have been detected in samples taken from oral malignant tumors and serum of patients with this condition, linking this to the risk of promoting carcinogenesis.[14] Persistent inflammation affects the microbiota, consistent with an imbalance of the microbial environment of the oral cavity. Such conditions can be a substrate for the onset of mucosal diseases, including cancers derived from them.[15] In addition, an association has been shown between the simultaneous use of a pro-inflammatory diet and cigarette smoking and an increased risk of developing squamous cell carcinoma in the head and neck region.[15]

Foods with significant inflammatory potential include highly processed, smoked and highly heat-treated products. The agents with proven mutagenic and carcinogenic potential contained in meat products include aromatic hydrocarbons (PAHs) and heterocyclic aromatic amines (HAAs). Under the influence of cytochrome P450, they are activated, resulting in compounds with strong carcinogenic and oncogenic potential. Due to their reactivity to DNA and proteins, they can predispose to genetic mutations, exacerbate oxidative stress and consequently damage cells.[16] The level of PAHs in meat depends on the preparation and heat treatment method used.

Smoked and grilled products have a higher content of harmful aromatic hydrocarbons.[17] This is related to the deposition on their surface of compounds formed in the process of incomplete combustion.

A diet with low inflammatory potential is based on products whose consumption helps reduce the harmful effects of chronic inflammation. Polyphenols are a group of phenolic compounds including flavonoids, phenolic acids, resveratrol, lignans and ellagic acid. They are found in products of plant origin - they can be found in fruits, vegetables, tea, chocolate and cereals. The health-promoting effects of polyphenols are based on limiting cell and tumor growth by inducing apoptosis and inhibiting angiogenesis.[18] They participate in the reduction of oxygen free radicals, helping to reduce the negative effects of oxidative stress on biochemical processes.[19] In addition, they are directly involved in regulating the immune system by increasing the anti-tumor potential of Natural Killer cells, promoting the maturation of immune cells or enhancing cytotoxic activity.[20]

An interesting issue linking diet and stimulants to the development of oral cancer is the consumption of wine. The grapes that are the basis for its production are a rich source of polyphenols, including catechins from the flavonoid group also found in green tea.[21] Their presence reduces the negative effects of a pro-inflammatory diet on the oral epithelium, thereby reducing the risk of various diseases. The content of individual phenolic compounds varies depending on the type of wine, which implies the health effects associated with its consumption. However, it is worth remembering that one of the main components of wine remains ethanol, which has been singled out as a risk factor for the development of malignant tumors in the head and neck region. The products formed in the body as a result of its metabolism disrupt the biochemical processes of cells, contributing to their damage and the formation of abnormal lineages. In addition, they can abolish the positive effects of polyphenols on the oral mucosa.[21,22] Due to the divergent results of studies determining the contribution of wine to the risk of carcinogenesis, the topic is controversial in the scientific community and requires further verification.

Tobacco

The best described, and most important, risk factor for developing oral cancer is tobacco use, both in the form of cigarettes and smokeless tobacco. Tobacco is the leading cause of premature death worldwide.[23] A number of IARC Group 1 carcinogens (substances classified as human carcinogens) have been described in common cigarettes, among them arsenic, formaldehyde, or NNK (Nicotine-Derived Nitrosamine Ketone) and NNN (N′-nitrosonornicotine).[24]

Carcinogenic nitrosamines and polycyclic aromatic hydrocarbons (PAHs) can also be found in smokeless tobacco.[25]

One of the most notable chemical compounds belonging to PAH is benzo[a]pyrene, which is metabolized by cytochrome P450 to the carcinogenic and toxic 7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (BPDE), which results in the formation of DNA adducts, mainly purine (guanosine and to a lesser extent adenosine), leading to mutation and DNA damage.[26] In addition, PAH metabolism causes the release of reactive oxygen species (ROS), thereby contributing to oxidative stress,[26] which can also play a role in the process of carcinogenesis, leading to genomic instability and thus subsequent DNA damage.[27] At the same time, benzo[a]pyrene has been shown to contribute to a decrease in antioxidants such as vitamin A and vitamin E, as well as a decrease in reduced glutathione levels, while causing an increase in pro-inflammatory cytokines.[27]

Chronic exposure to these substances results in DNA damage and an increase in the proliferation rate of oral epithelial cells,[5] which can subsequently lead to the development of precancerous lesions and oral cancer.

The negative effect of tobacco has been shown to depend on the dose of tobacco and the length of exposure.[28] A study by Polesel et al.[29] estimated that smoking as few as 2 cigarettes per day contributes to a significant increase in oral cancer risk.

Quitting smoking reduces the risk of developing cancer, although the relative risk (RR) does not return to the same level as in never-smokers until after at least 20 years of non-smoking.[30]

Among smokeless tobacco, chewing tobacco is the most important risk factor.[31] According to WHO estimates, Southeast Asian countries account for about 90% of all smokeless tobacco use in the world, this is especially true in India and Bangladesh, where chewing tobacco use is very popular, both among men and women.[32] This is reflected in the incidence of oral cancer, as India and Bangladesh are the countries with the highest incidence of the disease.[33]

An interesting issue is the increasing use of e-cigarettes these days, which were initially touted as a safer alternative to classic cigarettes, but there are more and more studies emerging that cast doubt on their apparent "safety." According to available research, e-cigarettes also contain substances described as carcinogens such as formaldehyde and heavy metals.[34] In-vitro studies show that the components of e-cigarettes can cause oxidative stress in cells, as is the case with classic cigarettes or chewing tobacco.[35] In addition, they cause damage to the genetic material of oral epithelial cells, and are thus genotoxic and cytotoxic.[36] Although further research is required on the effects of electronic devices on the development of oral cancer, cases of oral

cancer in e-cigarette abusers have been described, despite the absence of other risk factors known to date.[35]

Alcohol

Alcohol is one of the most widely consumed intoxicating substances among the global population. According to a WHO report (2018), in 2016, alcohol consumption per person aged 15 or older was 6.4 liters worldwide.[37] Due to the widespread prevalence of this stimulant, it has begun to be studied for its effects on health and the development of diseases, including head and neck cancers.

Ethanol is metabolized by alcohol dehydrogenase (ADH), cytochrome P450 2E1 and bacterial catalase to acetaldehyde. In the conducted studies, it was shown to be highly reactive towards the cell's DNA. Its binding to DNA leads to the formation of defective adducts, which increase the risk of mutations, double-strand breaks or structural changes in chromosomes.[38] Thus, the effects of acetaldehyde may underlie carcinogenesis and cancer development.

Alcohol consumption shows a correlation with increased oxidative stress[39] by interfering with the body's metabolic processes: acetaldehyde can interact with proteins and lipids, leading to the formation of reactive oxygen species (ROS);[40] alcohol impairs the immune system response by disrupting the normal cytokine production pathway and activating a number of biochemical mechanisms;[41] ethanol metabolism is responsible for increasing the activity of CYP21E, in effect contributing to excessive formation of ROS;[40] alcohol consumption contributes to a decrease in glutathione (GSH) levels, which is one of the most important protective factors against lipid peroxidation.[39]

The amount of alcohol intake translates directly into the risk of developing oral cancer. According to studies, it has been shown that low or moderate intake does not significantly affect the promotion of carcinogenesis. On the other hand, high consumption exceeding 30 grams of ethanol per day may be a significant risk factor. The strongest association between alcohol and cases of oral malignancies was observed among study subjects taking > 50 grams of ethanol per day.[21,42]

An important risk factor in the development of oral cancer is the synergistic effect of alcohol and tobacco. It has been shown that people who simultaneously consume alcohol and smoke cigarettes are at higher risk of the carcinogenic effects of these substances.[43] For example, consumption of > 40 drinks per week and a history of > 45 pack-years increases the risk of oral cancer 14 times that of non-drinkers and non-smokers. In contrast, a history of > 45 pack-years combined with significantly lower alcohol consumption (<10 per week) is associated with an approximately 3-fold increase compared to nonsmokers.[44]

Betel

Betel and its effects on health are of interest in the fields of epidemiology, dentistry and oncology. The culture of taking this substance is closely related to the areca (*Areca catechu sp.*) growing area, which is found primarily in South Asian and Southeast Asian countries. According to available data, areca nuts are used by about 600 million people, which ranks it 4th among the most widely used stimulants worldwide.[45] Due to this wide prevalence and strong regionalization, people have begun to look for links between habitual betel chewing and the risk of developing oral diseases.

The main ingredient used to produce betel is areca nuts. The extract obtained from them is rich not only in saccharides, polyphenols, fats or tannins, but also in components with proven harmful effects on health. Arecoline is categorized as an alkaloid from which nitroso compounds are formed with the participation of enzymes in saliva. Their presence is an important inducer of oral lesions.[46] Both of these groups show potential carcinogenic effects, which may translate into an increased risk of developing cancers in the head. The deleterious effect of arecoline causes a reduction in the expression of the p53 protein, thus being responsible for the disruption of the tumor suppression pathway. It has been proven to negatively affect the course of cell division by damaging DNA strands, creating chromosomal aberrations and disrupting the exchange of sister chromatids.[47]

Betel chewing plays a significant role in the development of diseases of the head and neck region, including precancerous conditions. Complications of chronic areca nut use include submucosal fibrosis, which occurs as a result of increased collagen production and reduced extracellular degradation. This mechanism is due to the action of arecalin modifying the metabolic pathways of the cell. It has been shown to be responsible for increasing the levels of transforming growth factor beta1 and TIMP1 while inhibiting gelatinase A.[46,48] According to available epidemiological studies, submucosal fibrosis will undergo malignant transformation in 2-13% of cases.[49]

The neoplastic transformation of oral precancerous conditions depends on the co-occurrence of several risk factors. Among the most important are the severity of oxidative stress, tissue hypoxia, damaging reactivity to cell DNA, and CYP polymorphisms. Arekaline exhibits strong oxygen free radical-promoting effects by affecting cytochrome P450 and NADPH oxidase enzymes. In addition, it inhibits superoxide dismutase activity, reducing the body's antioxidant capacity.[46] Alkaloids in areca nuts play a role in increasing inflammation by increasing the production of cytokines and pro-inflammatory markers.[50] Promotion of epithelial-mesenchymal

transformation is also an important risk factor for the development and expansion of oral cancer.[51]

Discussion

In the above study, we summarized the role of diet, alcohol, betel and tobacco in different forms on the increased risk of developing oral cancer. These factors are important to identify because they are modifiable or removable, which could probably result in a significant reduction in the occurrence of this cancer worldwide. Although awareness of the harmfulness of stimulants such as alcohol and cigarettes is widespread, relatively little attention is still paid to their role in promoting oral cancer. It is essential to educate the community on this issue, due to the ever-increasing number of cases. The use of electronic cigarettes and their potential carcinogenic effect should also be leaned into, which is a new challenge in oncology and dentistry.

Conclusion

Oral cancer is a serious medical problem of global concern. For this reason, detailing the risk factors associated with dietary habits and stimulant intake is of great importance in cancer prevention. Studies conducted to date have shown that the use of a pro-inflammatory diet is among the strong factors that increase the risk of malignant cancer. In order to counteract the negative impact of highly processed products and those subjected to harmful heat treatment, it is worth reducing their share in daily meals. In turn, protective compounds, which include polyphenols contained in plants, exhibit a number of health-promoting properties, so they support the proper functioning of the body.

An important aspect that determines the risk of developing oral cancer is the intake of stimulants. Their habitual and chronic use has a direct impact on the disruption of biochemical and metabolic processes taking place in the cells of the mucous membranes. Tobacco and alcohol are potent carcinogens, and their global prevalence poses a huge challenge to medicine in terms of prevention. Betel chewing, on the other hand, shows a strong correlation with areca nut consumption, which translates into a marked increase in new cases of oral diseases in specific geographic areas.

The results obtained in the review helped isolate harmful substances and those with preventive effects, which can significantly reduce morbidity and improve survival rates. Therefore, awareness of potential risk factors for head and neck malignancies should be increased.

DISCLOSURE

Author's contribution

Conceptualization, Magdalena Kras and Katarzyna Lelek; methodology, Dominika Poborowska; software, Katarzyna Polańska; check, Marta Wojaczek and Weronika Kahan; formal analysis, Marcin Łata and Katarzyna Polańska; investigation, Marcin Łata and Agnieszka Kosińska; resources, Katarzyna Lelek; data curation, Magdalena Kras; writing - rough preparation, Dominika Poborowska; writing - review and editing, Marta Wojaczek; visualization, Piotr Niedbał; supervision, Agnieszka Kosińska and Piotr Niedbał; project administration, Weronika Szafrańska and Weronika Kahan ; receiving funding - no specific funding.

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Conflict of interest

The authors deny any conflict of interest

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