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Etiology and Associations of Oral and Oropharyngeal Cancer

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Abstract

This research paper discusses oral cavity cancer, which is one of the 11th most common cancers in the world. According to newer research, some important possible causes include smokeless tobacco, marijuana, and citrus fruits. Some research attributes it to one's genetic makeup and include exposure to Human Papillomavirus (HPV) and diagnosis of Diabetes mellitus, all in conjunction with one's age. In this research paper, each of these factors are discussed in depth, and their association with this illness is considered and debated. Review of the literature reveals that the high concentrations of nicotine found in smokeless tobacco products is deleterious to oral health. Citrus fruits have been shown to prevent oral cancer. Multiple studies reviewed implicated HPV-16 and HPV-18 as having a gross etiologic role in many cancers of the oropharynx and the oral cavity. The causes for this cancer have been previously attributed to inaccurate, or unclear factors. This paper works to identify some unfamiliar factors that could quite possibly be important risk factors for this illness. Much of this research is fairly new and requires additional studies to substantiate the causes and help raise awareness, especially in lesser developed countries.

Introduction

Cancers of the oral cavity are the 11th most common cancers in the world. About 145,000 deaths were estimated to have occurred in 2018 across all areas of the globe. Etiology of most cancers that occur in the mouth has been attributed to a complex interplay of genetic and environmental factors, as with almost all other types of cancer. Some of the more well known and preventable causes include smoking and excessive alcohol consumption. However, though the rate of cigar and cigarette smoking have trended downwards throughout the world, the rate of cancer associated with the oral cavity has steadily increased (Warnakulasuriya, 2020). Therefore, it is imperative to explore the many other, less known, risk factors that are associated with oral cancer. In the last ten years much research has been conducted regarding cancers that affect the oral cavity and new, surprising associations have come to light. Many of these associations are environmental factors that can be eliminated including smokeless tobacco, marijuana, and citrus food intake. Other associations are related to one's genetic makeup and include exposure to Human Papillomavirus (HPV) diagnosis of Diabetes mellitus, all in conjunction with one's age (Petersen, 2009).

Before one can explore the many potential causes of oral cancer, it is important to understand the types of soft tissue cancer that can be found in the oral cavity. Ninety percent of all cancers found in the oral cavity are Squamous cell carcinomas (SCC). Squamous cells line most of the oral cavity and provide a smooth and protective layer to the mouth. The other ten percent of cancers that occur in the oral cavity include Verrucous carcinomas, minor salivary gland carcinomas, Lymphomas, and many benign tumors including granular cell tumors, fibromas, and granulomas. Minor salivary gland tumors, as the name suggests, affect the many minor salivary glands that are found in the hard palate (60%), lips (25%) and buccal mucosa (15%). Subtypes of this type of carcinoma include adenoid cystic carcinoma, mucoepidermoid carcinoma and polymorphous low-grade adenocarcinoma. Lymphomas of the oral cavity develop in lymphatic tissue found in the tonsils and the posterior 1/3 of the tongue. Additionally, some of the benign tumors found in the mouth have a tendency to become malignant over time and are often excised as a precaution. The final group of soft tissue cancer of the oral cavity includes mucosal melanomas (Scully and Porter, 2001). These can often be found at the vermilion border or the hard palate and can be locally aggressive.

Dentists and oral pathologists have identified key premalignant lesions that have a strong association with SCC. These lesions include leukoplakias, erythroplakias, oral lichen planus, and oral submucous fibroses. The WHO (2018) further classifies these according to degree of dysplasia; mild, moderate, severe, and carcinoma in situ. Leukoplakias are simply defined as a "white patch or plaque that cannot be characterized clinically or pathologically as any other disease" (Van der Waal, 2015). It is important to note that these lesions or patches are not wipeable. Lesions of this nature that can be wiped away are often fungal related like Candidiasis albicans. About 2-5% of leukoplakias annually go on to become malignant. Dentists and health care providers will often biopsy these lesions and monitor them consistently for changes in color or size. One of the biggest risk factors for malignancy is the location of lesion. Lateral borders of the tongue and the floor of the mouth are known to be the most common areas for malignancy to appear. Erythroplakia is defined as a "bright red velvety patch that cannot be characterized clinically or pathologically as being caused by any other condition" (Van der Waal, 2015). These have a much higher malignant potential than leukoplakias and are mostly associated with severe dysplasia and carcinoma in situ. These will generally be excised entirely and biopsied.

The goal of this paper is to delve into the research surrounding some of the stronger environmental and genetic associations of oral and oropharyngeal cancers. The topics covered will include citrus fruit intake, smokeless tobacco use, human papillomavirus, and inflammatory bowel diseases. Systematic reviews and meta-analysis will

be utilized to understand the possible pathophysiology behind these associations, along with their prevalence, and thoughts on preventative measures.

Citrus Fruits

Oral cancer accounts for over 3% of the overall burden of cancer globally, with an incidence of 350,000 cases in 2013. Patients with oral cancer have a poor prognosis despite advances in treatment as they continue to present with late-stage disease. Indeed, the 5-year survival rate for oral cancer is only 46% for men and 54% for women. In the last 10 years, many studies have provided evidence that a regular intake of citrus fruits is associated in prevention of oral cancer. A meta-analysis discusses results that indicate that there is an inverse association between citrus food intake and prevalence of oral and oral-pharyngeal cancers.

Seventeen studies were reviewed for this meta-analysis. The authors begin the review by listing the confounders each study controlled for. These include age, sex, BMI, smoking status, alcohol use, and education levels. Most studies gathered data from participants using a food frequency questionnaire. Meta-analysis was conducted by grouping participants with an increased risk of oral cancer based on their average citrus fruit intake. Upon statistical analysis of the pooled results, it was determined that participants had a maximum of 50% reduction in risk of oral cancer based on the degree of intake. (Cirmi, et. al., 2018)

The study also goes on to outline possible mechanisms by which citrus fruits can work to combat cancer. Citrus fruits are known to have high levels of Vitamin C. Vitamin C has been proven to combat inflammation and damage to DNA structures, which can initiate cancer. Furthermore, the antioxidant properties of Vitamin C work to kill cancer cells that may be proliferating (Grosso, et. al.,2013). Another hypothesis delves into the bioactive compounds that can be found in citrus fruits. These include flavonoids, carotenoids, and limonoids. Of these three, flavonoids are known to reduce inflammation, risk of infection, and oxidative stress. Oxidative stress and inflammation can lead to oxidative damage which works to initiate and promote cancer (Ravishankar, 2013). As such, both hypotheses conclude that the components of citrus fruits provide an antioxidant environment for the oral cavity and pharynx.

Smokeless Tobacco

Another important area of study in regard to oral cancer is the use of smokeless tobacco. This includes chewing (spit) tobacco, moist snuff and other tobacco containing products that are not smoked. Many wrongfully believe that the health concerns surrounding cigars and cigarettes are caused by the 'smoke' element. Thus, they believe chewing tobacco and snuff are a safer alternative. Nicotiana rustica and Nicotiana tabacum are the two major varieties of tobacco. Nicotine, a volatile alkaloid, is the most essential component obtained from the leaves of this herb. Nicotine is one of the most stimulating and harmful substances on the market. Nicotine affects all organs, and can bind to CNS receptors, and raises brain dopamine levels, rendering it a highly addictive substance. Muthukrishnan et al states, "Chewing tobacco and other smokeless tobacco products are known to be deleterious to oral health." His group has done much research in this field showing that smokeless tobacco has more deleterious negative effects on the oral cavity, in comparison to their smoke-fueled counterpart. They further detail the main health risks associated with smokeless tobacco, namely, oral squamous cell carcinoma (SCC), verrucous carcinomas, and tobacco-induced oral mucosal leukoplakia (Muthukrishnan , 2018).

Not only do SLTs contribute to cancer risks through their nicotine content, but they can also increase this risk by the oral abrasion they cause. Many abrasives are added to SLTs in order to accelerate nicotine absorption through oral mucosa. These abrasives wear down enamel, dentin and root surfaces along with the sensitive mucosal lining. Prolonged trauma to these sites can create irritation fibromas that have an increased malignant potential (Janbaz, 2014).

To further this idea, it has been documented by WHO that the country with the highest prevalence of oral and oropharyngeal cancer in the last 10 years is India. Oral cancer incidence rates in many parts of India surpass 6 per 100,000 males, and in some areas, they are as high as 10.8 per 100,000. About one-half of all tobacco used in India is smokeless tobacco, and nearly 100 million people use smokeless tobacco products daily. A study was conducted on this subject in India from October–November 2003. Indian smokeless tobacco products that were bought from retail stores in Gujarat, Karnataka, and Mumbai, India were quantified. Each purchase's date and location, as well as the batch number, were recorded. The 32 labels that were gathered for research are items that are widely used in India. There were also five common brands of non-tobacco chewing mixtures (supari) included. Analysis of both groups of recreational chewing products concluded that the SLT products not only had high levels of nicotine, but also excessively high levels of nitrosamines (nitrates), in comparison to levels of nitrates we have in foods like cold cuts and hot dogs. Nitrosamines are known to be carcinogenic in high volumes, as so may be contributing to the risk of oral cancer along with the nicotine. (Stepanov, 2005)

To reduce the morbidity and mortality associated with the use of these drugs, immediate public health interventions are needed. It is both ironic and disheartening to realize that many third-world countries lack so much health literacy that people are choosing nicotine options that are actually worse for one's health, thinking that they are opting for the 'healthier' alternative. Ideally, advocacy campaigns to strengthen and enforce policies restricting SLT and smoking are needed in most of Southeast Asian countries, but these efforts require more resources, which many countries just cannot support at this time.

Human Papillomavirus

The Human Papillomavirus is an ancient pathogen infecting epithelial tissues in amphibians, reptiles, and mammals. Its composition includes a double-stranded DNA surrounded by a protein capsid, similar to many other viruses on the Papovaviridae family. There are more than thirty strains of this virus, of which a fourth are associated with oropharyngeal cancers. The most common low risk strains found in HPV-related oropharyngeal cancer are HPV- 6 and 11, while the most common high-risk strains are 16 and 18. The high-risk strains are mainly transmitted via frequent vaginal and/or oral sex with multiple partners and without barrier usage. The pathophysiology behind this virus is mainly a result of its oncoprotein production. HPV protein E6 has been shown to interfere with p53 mechanisms in the body and protein E7 interferes with pRb tumor suppressor protein in the host. These interruptions lead to abnormal cell growth by inhibiting the apoptosis pathways and dysregulating the cell cycle. As such, the early HPV oncoproteins E6 and E7 are responsible for the malignant phenotype.

It is important to appreciate the nuisances between HPV related oropharyngeal cancers and non-HPV related ones. The most critical difference can be seen in the detection and initial manifestations. Most HPV associated oropharyngeal cancers begin with a protruding neck mass, while non-HPV related ones often begin with symptoms of sore throat and dysphagia. Research has also shown that oropharyngeal cancers associated with HPV have a much better prognosis, but the end-term side-effects can be more drastic (Timbang, 2019). As the oropharynx regulates speech, swallowing reflexes, and airway patency, surgery or other medical treatments in the area pose substantial risk of morbidity. Standard treatment for HPV related oral and oropharyngeal cancers is currently chemotherapy, radiation and sometimes surgery. The after-effects of these procedures often wreak havoc on the oral cavity. Xerostomia, worsening periodontal condition, loss of taste, trismus and osteoradionecrosis are only some of the risks involved after treatment.

Several studies have looked into the prevalence of HPV in oropharyngeal cancers, but HPV identification rates vary widely based on the population, subsite combinations, specimen type, and detection process. HPV is more commonly seen in oropharyngeal and tonsillar cancers than in other head and neck cancers. One study provides a clear and insightful connection between HPV and oropharyngeal cancer (Herrero, 2003). From April 1996 to December 1999, the research was conducted in Italy, Spain, Northern Ireland, Poland, India, Cuba, Canada, Australia, and Sudan. Patients were recruited from cancer referral clinics, and control groups were drawn from the same clinics or nearby general hospitals that served the same populations as the case patients. Control subjects were chosen based on sex and were within a 5-year age gap from the case participant. Control participants were disqualified if they had a history of oral cavity or oropharyngeal disease.

Their methods included obtaining an interview, collecting exfoliated oral cells, bloodwork, and biopsy specimen from all case patients. HPV DNA was detected by polymerase chain reaction testing (PCR). The results indicate that HPV DNA was detected in 3.9% of biopsy specimens of 766 cancers of the oral cavity and of 142 cancers of the oropharynx. HPV DNA in cancer biopsy specimens was detected more frequently among subjects who reported more than one sexual partner or who practiced oral sex. HPV-16 DNA was found in 94.7% of HPV DNA-positive case patients. Their conclusion was that HPV, especially strain HPV-16, plays an important etiologic role in many cancers of the oropharynx and the oral cavity. However, there is still uncertainty regarding the mechanism of transmission, that requires further investigation.

In the last ten years much headway has been made in terms of prevention of HPV-related cancers of the oropharynx and oral cavity. Public health campaigns have been instituted to increase barrier contraceptive use when engaging in oro-genital intercourse. Much of this is based on the vast amount of research implicating HPV16 and 18 in cancers of the oral cavity and oropharynx. These campaigns are especially geared towards older adults who are beyond the vaccination age. In terms of vaccination, the first vaccine related to HPV was released in 2006 by the CDC and called Gardasil-4. This vaccine protects against the four main strains implicated in HPV-related cervical cancer in women. Recently a newer version of this vaccine was released, preventing against 9 different strains, and covering over 90% of strains implicated in cervical cancer. The initial roll out of this vaccine was geared towards boys and girls ages 9-26, with the optimal

administration at 11 or 12 years of age. The idea behind this was to administer the vaccine prior to initiation of sexual activity and at an age when the body has the strongest immune response. Since then, the age recommendation has increased to 45 years old, though its efficacy at this older point in life is exceedingly less.

It is important to note that the CDC has not approved the vaccine for fighting oropharyngeal cancers related to HPV. This stems from a broad lack of knowledge in the medical world regarding cancers of the head and neck. When surveyed, 15.5% of members of the Louisiana Chapter of the American Academy of Pediatrics were not aware of the link between oral cancer and HPV, and less than half knew its prevalence in this country (Mehta, 2017). One of the main reasons the CDC has chosen not to endorse vaccines for HPV related oral cancers is because this type of cancer may not develop for many years after initial infection with the virus. As such, clinical trials establishing correlation between increasing vaccine use and decreasing oral cancer rates may be exceedingly difficult. Another critical distinction between oral and cervical cancers related to HPV is detection. Papanicolaou tests for cervical cancer are administered regularly and with high accuracy. No similar test with the same acuity is available for oropharyngeal cancers. As such, this vaccine may be the strongest form of prevention.

Inflammatory Bowel Diseases

Inflammatory bowel diseases has also been associated with oral cancers. Inflammatory bowel disease (IBD) refers to two diseases, Crohn's disease, and Ulcerative Colitis, under which the gastrointestinal (GI) tract is inflamed over a long time. While the exact cause of IBD is unclear, it is caused by a malfunctioning immune system. To defend the body, a fully functioning immune system destroys infectious species such as viruses and bacteria. The immune system reacts inappropriately to environmental stimuli in IBD, resulting in gastrointestinal inflammation. There tends to be a genetic factor as well, with someone who has a family history of IBD being more likely to have this abnormal immune response. Much research has been conducted on this subject in relation to the field of dentistry to understand oral manifestations of IBD, and if there are any links between the disease and oral/oropharyngeal cancer.

One study, compared subjects with Ulcerative Colitis and Crohn's Disease in comparison to a healthy control group. The goal of this study was to understand whether IBD has an effect on the oral cavity. The case group was divided into five classes based on their medication and treatment regimen: untreated, salicylate treatment, corticosteroid therapy, immunosuppressant medications (azathioprine and cyclosporine), and biological therapy (infliximab and adalimumab). Patients who agreed to participate in the study completed a structured questionnaire that asked about their age, ethnicity, medical background, medications, smoking habits, and oral hygiene habits. Patients were also asked to mention any unusual oral manifestations they experience, such as xerostomia, halitosis, dysphagia, regurgitation, and dysgeusia, as well as other signs of oropharyngeal cancer.

The results garnered indicate a higher incidence of oral manifestations as well as oral and oropharyngeal cancer in the case group vs the control group, though statistical significance was not achieved. They also noted that the majority of complications were seen in the corticosteroid and immunosuppressant therapy groups. However, the authors state, somewhat confusingly, that the pharmacological therapy of IBD did not show a statistically significant relation with the presence of lesions of the oral mucosa or oral cancer (Laranjeira, 2015). This is difficult to understand when the untreated group did not show any signs of oral manifestations. As such, much of this data fails to serve clinical significance.

A recently published systematic review on this topic works to provide a pathophysiology behind IBD and cancers of the oral cavity and oropharynx. Their search strategy included PubMed, Embase, and Scopus articles on this topic from 1946 to January 2015, published in any language. The results of this study indicate that the connection between IBD and oral cancers are the extensive use of immunosuppressive drugs in this patient population. "Immunosuppressants may promote cancers by various mechanisms including carcinogenic mutations of cell DNA, impaired immunosurveillance of tumor cells, impaired number or function of immune cells chronically infected by Epstein-Barr Virus [EBV] or HPV, and several others (Katsanos, 2016)."

As such, prolonged immunosuppression for chronic graft-vs-host disease or IBD increases the risk of oral cancer. It is important to note that oral cancerous and precancerous lesions have been reported in patients with IBD as reported for other groups of immunosuppressed or transplanted patients. Unfortunately, there are no precautions implemented to modify this risk and there are no routine oral cancer screenings recommended for this patient population. It would behoove the medical and dental communities to collaborate on ways to manage the increased risks faced by people undergoing immunosuppressant treatment for IBD and other conditions involving immunosuppression.

Conclusion

Many lesser known and novel causes of oral cancer and oropharyngeal cancer were discussed in this literature review. The purpose of this was to broaden our understanding of the disease and consider possible etiologies that had not been associated with the oral cavity in the past. With this knowledge, we can better educate the public in preventative measures as well as encourage more routine screenings for those practicing higher risk behaviors. As the saying goes, prevention is the best form of treatment.

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