Review Article

Sex hormones in gender-specific risk for head and neck cancer: A review

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Abstract

Despite the fact that numerous researches have been carried out to prevent head and neck cancer (HNC) and treat those patients, there is no reduction in morbidity rate because the underlying molecular pathogenesis is still poorly understood. Endocrine microenvironment is another vital factor besides other traditional risk factors like tobacco smoking, infections, and alcohol. It has been proven that sex hormone receptors are also expressed in larynx and lungs, in addition to sex organs. Sex hormones play a vital role in gene expression involved in the plethora of biological and neoplastic processes. The role of sex hormones in HNC is still divisive and very few researches have been conducted to describe their role. So, this article is an effort to attract the attention of researchers, endocrinologists, pathologists, and clinicians toward the impending role of sex hormones, with special emphasis on progesterone, estrogen, and prolactin in HNC onset and progression, along with their therapeutic role.

Key words: *Endocrine hormones, head and neck cancer, oral, sex*

INTRODUCTION

Head and neck cancers (HNCs) include cancers of the upper aerodigestive tract (including the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx), the paranasal sinuses, and the salivary glands. HNC affects more than 550,000 individuals worldwide and around 50,000 in the United States annually.[1,2]

Most patients with HNC have metastatic disease at the time of diagnosis (regional nodal involvement in 43% and distant metastasis in 10%). The male to female ratio is currently 3:1 for oral cavity and pharyngeal cancers. Men are three times more likely to develop human papillomavirus (HPV)-associated HNC; this imbalance in epidemiology is expected to become more pronounced in the next 20 years.[2]

Tobacco, alcohol, and infections are considered as the main established factors associated with HNC. Substantive evidences revealed that there is considerable lack of association between HNC cases and exposure to these traditional risk factors, which lead to hypothesize the potential role of additional genetic and/or environmental factors.[3-5] A recent study showed that 75% of HNC patients who were non-smokers and non-drinkers developed squamous cell carcinoma of the tongue not associated with HPV and were females.[3] Recent data from this study group suggested that in addition to the major established risk factors, female hormones may also contribute to head and neck carcinogenesis and it strongly suggests endocrine involvement in its development.

The gender-specific risk for HNC raises different perspectives. Firstly, there are some detrimental factors affecting selectively only male patients. Secondly, there

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are common risk factors which affect both the genders, but females have some inbuilt defense mechanisms owing to their special metabolic and hormonal features.[6]

Endocrine environment plays a significant role in the progression of cancers involving sex hormone receptors, such as prostate, breast, and endometrial cancers. Since the sex hormone receptors also reside outside the sexual organs such as the larynx or the lung epithelium, they can be expected to play a vital role in various other cancer types also.[7]

Though the role of sex hormones in HNC is controversial and a topic of debate, this article is an effort to attract the attention of researchers toward their impending role in HNC.

SELECTION OF DATA

We conducted a comprehensive literature search related to sex hormones in HNC, sex hormones and oral cancer, and estrogen in HNC or oral cancer using PubMed and Medline databases.

Role of estrogen and progesterone in HNC

Studies on a large series of HNC patients have shown that the estrogen levels in females play a protective role in developing cancer. As males have lesser level of estrogen, they are more predisposed to develop cancer. Moreover, destruction of liver function in alcoholics leads to alteration in the metabolism of sex hormones (estrogen and testosterone). So, alcoholic males are at a higher risk of developing cancer than non-alcoholics. A large number of HNC patients are males, characterized by an endocrine milieu rich in testosterone sex hormone.[8,9]

Lukits *et al*.[7] demonstrated the presence of estrogen as well as progesterone receptors in oral cavity, laryngeal, or hypopharyngeal cancers at mRNA as well as protein levels. Alcoholic patients with chronic liver disease have altered metabolism of sex hormones involving testosterone and estrogen and are observed to be at risk for HNC.[7] Colella *et al*.[9] demonstrated that HNC patients have altered estrogen metabolism which may represent a risk factor for cancer development. They demonstrated varied expression of androgen receptor (AR) and estrogen receptor-alpha (ER-α) mRNAs in the malignant tissues of oral mucosa and suggest an interference of these sex hormones in HNC. Various metabolic end products of estrogen are shown to have genotoxic, mutagenic, transforming, and carcinogenic effects.[10] Schuller *et al*. demonstrated that a number of estrogen metabolism genes reside on the cells derived from HNC.[11] Another study group indicated that the altered metabolism of estrogen in the lung tissue as a result of tobacco smoke exposure can lead to development of cancers of the aerodigestive tract.[12]

So, estrogen can be considered as one of the imperative factors responsible for the development of HNC.

Role of other hormones

Recently, Bauernhofer demonstrated that elevated prolactin levels in HNC can be a marker of poor prognosis.[13] Bhatavdekar *et al*.[14] also demonstrated increased levels of follicular stimulating hormone (FSH), luteinizing hormone (LH), and prolactin, and decreased ratio of testosterone: Estradiol in tongue cancer patients. These hormonal fluctuations clearly indicated a disruption in the pituitary–adrenal–testicular axis. Thereof, it is suggested that these hormones might play a crucial role in the development and progression of oral cancer.[14]

Sex hormones in salivary gland cancer

Although a number of studies on malignant salivary gland tumors have been published in English literature, the rationale for hormone therapy is still a contentious topic due to the unlike results and inadequate number of cases. Some recent reports have shown substantive evidences that certain salivary gland tumors are similar to breast cancer at cellular and molecular levels as well.[15] Both the tumors show similar expression of progesterone associated with tumor onset and progression.[16] *In vitro* studies have demonstrated that progesterone treatment inhibits proliferation of malignant cells in the salivary gland. In addition to this, the AR was also reported to be expressed in salivary gland tumors such as pleomorphic adenomas and in malignant tumors such as salivary duct carcinomas and basal cell adenocarcinomas, demonstrating molecular similarities with prostate tumors.[17] Williams *et al*. also described that most tumors originating from breast and salivary glands shared similar expression of estrogen receptor-beta (ER-β). They demonstrated that the patients whose tumors lacked ER-β were at higher risk for local recurrence.[18]

Therefore, targeting ER-β may become an effective therapeutic approach for the management of salivary duct carcinomas. Nasser *et al*. also observed the uniform expression of AR in malignant salivary gland tumors. They suggested a potential role for AR

in the histogenesis and possibly a useful treatment intervention in the management of malignant salivary gland tumors.[19]

Therapy of HNC

However, on account of the promising benefits of endocrine therapy in breast cancer by targeting sex steroid hormone receptor, its potential role in HNC has also been investigated and the results of completed clinical trials are eagerly awaited.[17] A recent study conducted on tongue carcinomas demonstrated that ER antagonist interferes with cell adhesion and ultimately results in cell death, which further prevents the growth and progression of the tumor.[14] Treatment with ER antagonists such as tamoxifen is shown to decrease the phosphorylation of focal adhesion kinase (FAK), leading to reduced phosphorylation of extracellular signal-related kinase (Erk) and mitogen-activated protein (MAP) kinase, which consequently disrupts tumor growth.[20] These results imply that estrogen inhibition can modulate and prevent invasion and metastasis of oral squamous cell carcinomas.

Future perspectives

Further studies at a molecular level and larger clinical trials are the need of the hour to determine which receptors should be targeted and when, and which modulators are used for this in the management of HNC patients. Since hormonal therapies may also have some adverse effects on the physiological processes, balance has to be maintained between the therapeutic benefits of such interventions and the potential adverse effects.[21] Genome sequencing in association with proteomics could be helpful to define and select useful genetic and molecular biomarkers to predict and maintain the progression of HNC in the near future. Identification of specific genetic, epigenetic, and metabolic disturbances, in unison with other conventional techniques in diagnosis and prognostication are required to make the treatment strategy effective.[22]

CONCLUSION

Endocrine microenvironment of the host has been proved to be one of the imperative factors in altering the onset and progression of HNC. Sex hormones play an imperative role in gene expression involved in several biological and neoplastic processes. Thorough understanding of the molecular biology through the developments in high-throughput technology heralds an era of personalized medicine.

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