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Carcinogenesis and Sex Hormones: A Review

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Abstract

Carcinogenesis has a multifactorial etiology. The underlying molecular pathogenesis is still poorly understood. Apart from major risk factors like tobacco, alcohol, infections, there have been some recent and less known factors like endocrine hormones. Sex hormones receptors lie outside sex organs in organs like larynx and lungs where they play a role in gene expression involved in lot of physiological and neoplastic processes. The present article is an attempt to highlight role of various sex hormones in development of carcinogenesis, particularly Head and Neck cancers (HNC).

Keywords: Sex hormones; Carcinogenesis; Head and Neck cancer

Introduction

A multicellular organism can thrive only when all its cells function in accordance with the rules that govern cell growth and reproduction. Why does a normal cell suddenly become a "rebel," breaking the rules, dividing recklessly, invading other tissues, usurping resources, and in some cases eventually killing the body in which it lives?

Cancer results from a series of molecular events that fundamentally alter the normal properties of cells. In cancer cells the normal control systems that prevent cell overgrowth and the invasion of other tissues are disabled. These altered cells divide and grow in the presence of signals that normally inhibit cell growth; therefore, they no longer require special signals to induce cell growth and division. As these cells grow they develop new characteristics, including changes in cell structure, decreased cell adhesion, and production of new enzymes. These heritable changes allow the cell and its progeny to divide and grow, even in the presence of normal cells that typically inhibit the growth of nearby cells. Such changes allow the cancer cells to spread and invade other tissues [1].

Cancer is one of the biggest threats to humans and animals, claiming 7.6 millions of human lives in 2008 and 13.2 million expected cancer deaths by 2030 [2]. Worldwide, HNC affects more than 550,000 individuals' annually [3]. Oral and oropharyngeal cancer is the sixth most common cancer worldwide. The annual estimated incidence is around 275,000 for oral and 130,300 for pharyngeal cancers [4]. Male to female ratio for cancer predilection ranges from 2:1 to 4:1. The incidence rate in males exceeds 20 per 100,000 in different parts of world including India and United States [5]. Treatment for oral cancer is particularly disabling and disfiguring and disrupts the core aspects of daily life.

Oral cancer describes malignancies of the oral cavity, including structures such as the gingiva, buccal mucosa, hard palate, floor of mouth, salivary glands and anterior two-thirds of the tongue Cancers of the oropharynx and oral cavity share several risk factors, and the term 'head and neck cancer' (excluding nasopharyngeal carcinoma) is commonly used to define cancers of the oral cavity and oropharynx. There are multiple causes that lead to cancer development in an individual. Recent literature suggests that apart from the major established risk factors, female sex hormones may contribute to head and neck carcinogenesis and it strongly suggests certain endocrine involvement in its development [6].

Head and neck cancers are associated in most of the individuals who consume tobacco, arecanut, betel quid and alcohol with history of their long term usage. Latest studies revealed that in some cases of squamous cell carcinoma, a predominant viral etiology has been diagnosed, which were non tobacco and non-smoker group females [6] Head and neck carcinomas are also associated with exposure of traditional risk factors in addition to genetic and/or environmental factors [7-9].

Endocrinal hormones levels in both males as well as females plays a significant role in the etio-pathogenesis and progression of cancers of various organs that are associated with the sex hormones receptor like endometrial carcinoma, breast and prostate cancer, lung carcinoma [10]. Young females associated with certain disorders with hormonal imbalance like Polycystic Ovarian Disease (PCOD), have more potential risk in development of Ovarian cancer and endometrial carcinoma of uterus [11].

The gender specific risk for Head and Neck cancer (HNC) has different perspectives. Firstly because of some detrimental factors which affect only male patients. Secondly, there are common risk factors which affect both the genders, but females have some inbuilt defense mechanisms owing to their special metabolic and endocrine features [12]. More than 75% of cases of HNSCC are attributable to smoking and alcohol consumption. Smoking increases the risk by 10-fold compared with never smokers, and heavy alcohol intake is an independent risk factor [13]. The combined effect of tobacco and alcohol causes a greater multiplicative risk. Public health measures have been successful in reducing the use of tobacco, and therefore the incidence of HNSCC overall has been decreasing over the past 30 years in developed countries. However, there has been a dramatic increase in the incidence rates of oro-pharyngeal (tonsil and base of tongue) cancers because of infection with high-risk Human Papillomavirus (HPV) [14].

Physiology of Sex Hormones: A Brief Overview

A hormone (from Greek ὁρμή, "impetus") is a class of signaling molecules produced by glands in multicellular organisms that are transported by the circulatory system to target distant organs to regulate physiology and behavior [13].

Important Sex hormones of human body are estrogen, progesterone and testosterone, belonging to a group of steroid hormones, all of which are derivatives of cholesterol.

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Estrogen

Estrogens (ES) are female sex hormones, synthesized in the ovary, placenta, testes and adrenal cortex, contribute to the development and growth of female genital gender and female sex characteristics, and cause endometrial growth. Estrogens are considered to be one of the etiological factors of breast, uterine and ovarian tumors. It is also believed that they have an impact on other disorders, such as thrombo-embolic disease [14].

Types of estrogen:

1) Natural

2) Synthetic.

There are three basic, biologically active estrogens: Estrone (E1), 17-β Estradiol (E2) and Estriol (E3). Out of them main estrogen with highest biological activity is 17-β estradiol (E2) [15,16].

Testosterone

It is the principal male sex hormone, belong to androgen group and been secreted by testis of males and ovaries in females.

Progesterone

An endogenous steroid hormone involved in the menstrual cycle, pregnancy and embryogenesis of humans. It belongs to a group of steroid hormones called the progestogens and is the major progestogen in the body, plays an important role in brain function as a neurosteroid [17,18].

Effect of sex hormones on cancer development

The mechanism by which sex hormones affect cancer risk is probably largely (Figure 1) through determining the number and mitotic rate of the epithelial cells in the organ concerned [19]. High mitotic rates can increase cancer risk by increasing the chance of mutations occurring and of being replicated before they are repaired, and can also increase the growth of early tumours. In the case of estrogens, it has also been argued that certain metabolites of oestradiol may cause mutations by directly damaging the DNA, but the importance of this possible mechanism has not been established, and we think that the major role of sex hormones in cancer is likely to be as determinants of cell number and mitotic rate [20].

Androgen, estrogen and progesterone, acting through specific receptors, play an important role in the growth and development of several tumors, including breast, endometrium, and prostate carcinomas [21,22]. Additionally, patients with breast carcinomas positive to Estrogen Receptor (ER) and Progesterone Receptor (PgR) have been treated with antagonist hormones and shown decreased recurrences and higher survival rates. Similar results have been reported in patients with prostate cancer positive to Androgen Receptor (AR) [23,24].

Recently studies demonstrated that elevated prolactin levels in HNC can be a marker of poor prognosis [25]. Few other studies have demonstrated increased levels of FSH, LH, prolactin and decreased ratio of testosterone and estradiol in tongue cancer patients. These hormonal fluctuations clearly indicated towards 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 [26].

It was also reported that estrogen stimulates the proliferation and maturation of gingival connective tissue, epithelium and salivary glands [27]. ERs have been identified in a variety of human tumors rather than breast carcinomas using histochemical, immunohistochemical, and molecular biology techniques. Moreover, the expression of sex hormone receptors in certain tumors suggests a role for these receptors in tumor pathogenesis, progression and therapy. There is also direct evidence that the risk for some of these cancers is related to the circulating serum concentration of various sex hormones [28].

Direct influence of estrogen on target cells is caused by combining the steroid receptor complex with DNA. In that way, it can regulate the expression of genes and transform proto-oncogenes into oncogenes. Estrogens have two kinds of receptors – ERα and ERβ. They belong to the nuclear receptor superfamily of transcriptional activators. The affinity of receptors is different to different ligands, e.g. estradiol has a higher affinity for ERα than ERβ. Obesity causes an increase in serum concentrations of bio-available oestradiol, and this factor causes increases in the risk for both endometrial cancer and breast cancer [29].

Effect on head and neck cancers

Some recent reports have shown substantive evidences that certain salivary gland tumours are similar to breast cancer at cellular and molecular level as well [30]. Both the tumors show similar expression of progesterone associated with tumor onset and progression [31].

Estrogen may increase the movement of precancerous cells in the mouth and promote the spread of head and neck cancers. The results may help researchers to understand the risk factors that cause head and neck cancers in addition to the traditional risk factors of tobacco and alcohol exposure [32]. Squamous cell carcinoma of the head and neck (HNSCC), which include cancers of the tongue, mouth and throat, represent the sixth most common type of cancer and is known to be on the increase in some demographic groups, including young women without known risk factors. A recent report showed that 75% of young never-smoker/never drinker HNSCC patients who develop primary oral tongue squamous cell carcinoma are women, suggesting that female hormones may contribute to carcinogenesis [33].

Oestrogen has a strong impact on precancerous and cancerous cells. An earlier study showed that the oestrogen metabolism pathway is altered in lung tissue following tobacco smoke exposure, suggesting that oestrogen metabolism may play a role in the formation of other cancers of the aerodigestive tract [34].

Using cancer cells grown in the laboratory, the team found that oestrogen induced the expression of an enzyme called cytochrome P450 1B1 (CYP1B1) which is responsible for breaking down toxins and metabolising oestrogen. The CYP1B1 induction only occurred in precancerous cells and not in healthy cells or cells that had become cancerous [35,36].

Furthermore, investigators found that depleting the expression of CYP1B1 reduced the ability of precancerous cells to move and divide,

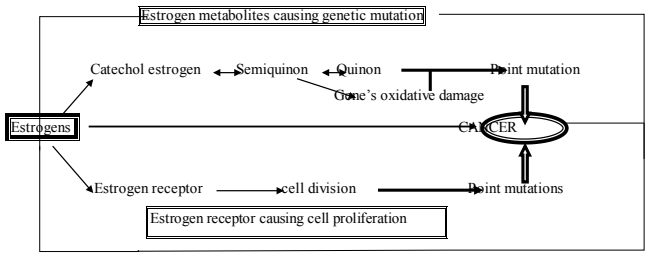

Figure 1: Mechanisms involved in carcinogenesis through sex hormones

in comparison with similar cells containing normal levels of CYP1B1. Oestrogen also reduced cell death in the precancerous cells, irrespective of the amount of CYP1B1 present.

Finally immune-histochemical staining of samples from patients with head and neck cancers showed that 91.9% stained positive for oestrogen receptor β, 99.4% for CYP1B1 and 88.4% for 17 β oestradiol.

"This study is the first to report the detection of estrogen within human head and neck tissue and demonstrate that both estrogen and CYP1B1 may contribute to the progression of HNSCCs," concluded the authors. They add that CYP1B1 levels may offer an important biomarker of tumorigenesis in head and neck cancers and present a novel target for chemo preventive interventions in patients with premalignant lesions [37,38]. Androgen is known to have an important role in the normal development and differentiation of a variety of cell and tissue types. This function is mediated by its binding to Androgen Receptor (AR), a member of the family of steroid hormone receptors. The presence of AR in a given cell type or organ system indicates a possible role for androgen in its growth and differentiation. AR mediates the effect of androgen by binding to specific DNA sequences and influences the transcription and translation of various genes. Fan et al suggested that AR may have a role in the pathogenesis of salivary duct carcinoma through the mediation of an epidermal growth factor receptor and transforming growth factor-α autocrine pathway similar to that seen in prostatic carcinoma [38].

Experimental studies have shown that androgen influences the expression of proto-oncogenes (like c-myc) and apoptotic factors (like the bcl-2 family) in lacrimal, salivary, and prostatic tissues of both mice and rats, as well as in cell line models. Whether the expression of AR in malignant salivary gland tumors indicates a role for androgen in the pathogenic process or simply represents an epiphenomenon of the malignant transformation remains to be determined.

Although partial remission of a salivary gland carcinoma following goserelin (an antiandrogen) therapy has been reported, this needs to be confirmed in a larger group of patients. It is been clearly demonstrated that there is a strong and consistent expression of AR exclusively in a sharply defined subset of malignant salivary gland tumors [39,40].

Clinical implications of head and neck cancer

Benefits of endocrine therapy in breast cancer by targeting sex steroid hormone receptor, its potential role in HNC are also tried and results of completed clinical trials are eagerly awaited [41]. Recent study conducted on tongue carcinomas demonstrated that ER antagonist interferes with cell adhesion and ultimately results in cell death which further prevents growth and progression of tumor [42]. 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 tumour growth [39].

Further studies at molecular level and larger clinical trials are need of the hour to determine which and when receptors should be targeted by means of which modulators in management of HNC patients. Since, hormonal therapies may also have some adverse effects on physiological processes, so balance has to be maintained between therapeutic benefit of such interventions and potential adverse effects [43]. Genome sequencing in association with proteomics could be helpful to define and select useful genetic and molecular biomarkers to predict and maintain progression of HNC in nearly future. Identification of specific genetic, epigenetic and metabolic disturbances, in unison with other conventional techniques in diagnosis and prognostication, are required to make effective treatment strategy [44].

Conclusion

Role of sex hormones is well established in cases of prostate, breast and endometrial carcinomas. Though the role of sex hormones in HNC is controversial and is debatable, so the present article is an attempt to highlight its impending role in HNC so that future studies can be performed on this less known entity.

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