



## Cancer in females: Are hormones the culprit?

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### ABSTRACT

Hormones are small chemical messengers that play a major role in the human body which helps in regulation, control of growth, development, reproduction, maintenance of internal environment and energy production. Genomic and non-genomic signaling mechanisms make hormones take special care in maintaining their concentration in serum and plasma. Women are highly prone to the hormonal imbalance due to many factors such as diet, sexual activity, endocrine disruptors and reproductive behavior. Dysregulation and irregular function of these hormones lead to the development of many diseases from cyst formation to cancer development. Hence it is necessary to understand the role and mechanisms of hormonal actions in cancer cells to target them as novel biomarkers for therapeutic strategies.

**Keywords:** Hormones, Endocrine, tumor, cancer, biomarkers, therapeutic

### INTRODUCTION

Endocrines are composed of ductless glands that secrete small molecules of the chemical messenger called "hormones". These hormones are involved in the response and regulation of cells by controlling the broad domains of human body functions such as reproduction, growth, development, maintenance of internal environment, energy production, utilization, and storage. Unlike other electrochemical signals of nervous systems, hormones secreted by the glands travels in the body by entering the blood stream and encounters special receptors with which they interact to initiate essential biological responses in specific tissues[1-2].

In general, the binding of the hormone to its specific receptor forms a complex so as to interact with the DNA which leads to the transcription and translation process resulting in the synthesis of protein. Many of these proteins are involved in the growth and proliferation of the cells and also governs about the cell division is regulated normally (healthy cells) or grows out of control (tumor cells). Along with the genomic pathways, they also involved in non-genomic pathways that often shows effects on metabolic systems within cells and in signaling between cells [3]. Because of these important roles in both metabolic and reproductive systems, it is necessary to carefully regulate their concentrations in serum. Most of the feedback systems between the hypothalamus and pituitary that maintain the level of circulating hormones. Further, the anabolism and catabolism of hormones are regulated by series of pathways specifically in the gland they secreted or the target they exert their effects. Any disruption in their synthesis or breakdown may affect the activity of natural hormones [4].

These disruptions can be any kind of environmental factors such as diet, sexual activity, and reproductive behavior that changes the "lifestyle". This lifestyle change in humans highly contributes to the imbalance in hormone level that may cause cancer such as "hormone-related cancers". Cell proliferation, differentiation, apoptosis are regulated and controlled by various factors like endogenous hormones and some growth factors. Dysregulation in any of these processes allows the cells to incorporate mutated proto-oncogenes and tumor suppressor genes that lead to cancer development [5]. Especially, female reproductive hormones play the major role in causing cancer due to their continuous exposure to female organs from the first menstrual cycle to menopause. In the case of cancer, it was

hypothesized that the endocrine manipulation can be one of the major cause of cancer. But still, the molecular mechanisms and development of cancer due to hormonal imbalance is unclear [1]. They themselves become a carcinogen by acting as a promoter for the malignancy or as an initiator [6]. It was reported that most of the female reproductive hormones are highly prone to the cancer development by enhancing the cell replication resulting in the chance of error in DNA copying, enhancing code-breaking action of sub-threshold doses of mutagens (virus, chemicals, radiation) and also it helps in unmasking latent DNA changes caused earlier by mutagens and few more [7-9].

Our aim is to review the knowledge on hormones responsible for the cancer development in women. This review is restricted to focus on some known female reproductive hormones such as estrogen, progesterone, androstenedione, prolactin and relaxin.

### Estrogen

In the late 19th century, Beatson demonstrated the association of estrogen and hormone-dependent cancers from a premenopausal woman. Further, the role of estrogen in tumor development has been marked as a promoter rather an initiator as it has the ability to stimulate the cell proliferation in the breast epithelial cells by causing DNA mutation [10]. Hypothetically it was said that the abnormal number of ovulatory cycles may increase the estrogen exposure to their target tissues resulting in increased rate of cell division and proliferation followed by an accumulation of random genetic errors. [11-12]. The biological synthesis of estrogen in the human body is based on three major synthesis mechanism such as conversion of androstenedione to estrone by an enzyme aromatase, hydrolysis of estrone sulfate to estrone by estrone sulfotransferase and reduction of estrone to 17 $\beta$ -estradiol by the enzyme 17 $\beta$ -estradiol hydroxysteroid dehydrogenase [13]. Estrogen upon synthesis they travel in the bloodstream and enters cells and nuclear membrane through passive diffusion. They binds to specific estrogen binding receptors, where estrogen binds and activates the specific sequences in the estrogen response elements which in turn regulates cell differentiation and proliferation [14]. It was believed that estrogen as an inducer, increase the cell proliferation and differentiation which also does the same for cells having mutated genes. Such genes that are involved in the risk of breast cancers are some of the oncogenes and tumor suppressor genes such as TP53, BRCA1, BRCA2, PTEN and ATM which are directly or indirectly influenced by estrogen hormone cascade mechanisms. Some of the studies have shown that estrogen and their catechol metabolites act as the carcinogen in various tissues which leads to the development of cancer. Estrogen metabolized through catechol pathway by several cytochrome P450 enzymes that produce 2-hydroxycatechol estrogen or 4-hydroxycatechol estrogen. Reduction of estrogen to catechols and quinones release some intermediate reactive oxygen species. That in turn damage fats, proteins and DNA. These observations support the hypothesis that oxidative metabolites of estrogen have genotoxic, mutagenic, transforming, and carcinogenic potential and thus could initiate or cause the progression of carcinogenic process in humans [15-21].

### Progesterone

Progesterone is an endogenous steroid hormone that involved in the menstrual cycle, pregnancy and embryogenesis. It acts as intermediate metabolite during the production of other steroids. It is also known as pregn-4-ene-3,20-dione. In humans, progesterone is synthesized from pregnenolone, derived from cholesterol. Conversion of pregnenolone to progesterone takes place as follows: first, the oxidation of 3-hydroxyl group to a keto group and then the double bond is moved to C4 to C5 by enol tautomerization reaction. The enzyme 3 $\beta$ -hydroxysteroid dehydrogenase/ $\delta$ (5)- $\delta$ (4)Isomerase has catalyzed the reaction. Further, the conversion of 17 $\alpha$ -hydroxyprogesterone to cortisol and androstenedione leads to the synthesis of testosterone, estradiol and estrone [21]. The synthesized progesterone enters the blood stream and involved in non-genomic signaling during fertilization. They also play an important role in lactation. Binding of progesterone to its specific progesterone receptor forms conformational changes and induce dimerization of the receptors. This activated receptors associate with co-regulators, and stimulates progesterone response element (PRE) and PRE-like sequences in the promoter regions of target genes such as C-myc, Fatty acid synthetase pathway etc [23]. It was investigated and reported that progesterone locally metabolized to certain compounds which are involved in stimulation or inhibition of cell proliferation and apoptosis. The enzyme 5  $\alpha$ -reductase converts progesterone to 5  $\alpha$ -pregnanes, e.g. 5  $\alpha$ -dihydro-progesterone (5  $\alpha$ -P), the 3  $\alpha$ -hydroxysteroid oxidoreductases and the 20  $\alpha$ -hydroxysteroid oxidoreductase metabolize progesterone to 3  $\alpha$ -dihydroprogesterone (3  $\alpha$ -HP) and 20  $\alpha$ -dihydroprogesterone (20  $\alpha$ -HP), respectively. Here the 5  $\alpha$ -P induce cell proliferation by involving in the MAP-kinase pathway whereas the metabolites 3  $\alpha$ -HP and 20  $\alpha$ -HP induce apoptosis and cell adhesion by stimulating the anti-mitogenic effect [24,25,26]. Hence it was mostly observed that the elevated or high level of 5  $\alpha$ -P in cancer tissue leads to the increase cell proliferation resulting in the metastatic breast or ovarian cancer. In some cases of ovarian cancer, it was found that the progesterone protects the normal cell from tumor development which is done by suppression of ovulation, in turn, it will reduce the elevated production of estrogen and subsequently reduce the exposure to serum estrogen. But still, the mechanism of action of progesterone is not well understood.

### Androstenedione

The potential importance of breast and ovarian cancer occurrence is through  $\Delta^4$ -Androstenedione. They easily transformed to estrone by the enzyme aromatase. Change in the lifestyle such as aging, diet, obesity is directly correlated with the rate of conversion of androstenedione to estrone. The other form of androstenedione, is  $\Delta^5$ -diol, a derivative from the DHEA that binds to the estrogen receptor in competition with estrogen and leads to the development of cancer in ovary and breast [27].

### Prolactin

Prolactin is a hormone that regulates lactation only. As a peptide hormone, these are secreted by the anterior pituitary gland and remains held till the period of lactation and infertility. The imbalance in hormonal level and occurrence of cancer in women has been suspected for many years. Recently its function and similarity to growth hormone through the growth promoting JAK/STAT pathway has given an idea on their relation in tumor promoting effects. The prolactin receptors are commonly seen in breast tissues of women. Though many targets and biomarkers have been identified still the search of factors that cause breast cancer remains to unveil. One such target of interest is prolactin where studies brought some concepts regarding the risk of cancer. (i) An elevated level of prolactin increases the risk of breast cancer, (ii) Evolution of breast cancer due to the locally produced prolactin that acts as autocrine or paracrine factors and (iii) is a casual relationship between the prolactin receptor and breast cancer. Recent studies also reported that the stimulation of estrogen in the synthesis of prolactin results in tumorigenesis. Hence if studies on prolactin, prolactin receptors and interaction with estrogen are studied widely there are chances for formulating treatment strategies [28-30].

### Relaxin

Relaxin, a natural peptide hormone having similar structure like insulin and insulin-like growth factors. They circulate in the corpus luteum of the ovary in women and rises to level within a 14 days period of ovulation. In a case of non-pregnant women results in menstruation. Also, its action includes promotion of growth and dilation of the cervix, growth and quiescence of the uterus, growth and development of the mammary gland and nipple, and regulation of cardiovascular function [31]. Also, evidence suggests that involvement of relaxin-like peptides in cancer. They are associated with various ways of cancer promotion including tumor cell proliferation, differentiation, invasion and neovascularization. Relaxin also helps in the remodeling of extracellular matrix in several reproductive tract tissues. It regulates the variety of gene expressions such as collagens, MMP1, vascular endothelial growth factor and cyclooxygenase-2. Also, relaxin helps in the catalytic activity of MMPs-1, 2, 3, and 9. They regulate the interaction with the plasminogen activator and tissue inhibitors of MMP in the extracellular matrix. Hence mutation in these genes or imbalance in hormone level may cause cancer by affecting the cell attachment, migration and invasion [32-35].

**Table 1. Endocrine disruptors: Action towards respective hormones**

Endocrine Disruptors	Action	Hormones
Diethylstilbestrol	Agonist	Estrogen, progesterone, Androgen
Dioxins and furans	Anti-estrogen	Estrogen, pregnane X receptor
Bisphenol A	Agonist	Estrogen
Genistein (phytoestrogen)	Activates transcription via ERE	Estrogen
Coumestrol (phytoestrogen)		Estrogen and Androgen
DDT and metabolites	Transcription activation by binding estrogen receptors; Anti-androgen	Estrogen and androgen
Dioxins	Activity of estrogen receptor by modulating through aryl hydrocarbon receptor; Blocks androgen-dependent proliferations	Estrogen and androgen
Carbaryl	Inhibits the action of hormones	Estrogen and progesterone
Chlordane		Testosterone and progesterone

### Endocrine disruptors and hormonal imbalance

Female reproductive tract tissues are key targets for the action of hormones such as estrogen, progesterone, androstenedione, prolactin, relaxin and others. All over the world malignancies caused in the female reproductive tract remains fourth most common cancers in women. Some of the cancers that are caused in women are breast, ovarian, endometrium, cervical, and vaginal tissues [37]. These are due to the various factors that lead to a hormonal imbalance in female organs specifically those that are exposed to hormones. The factors include oral contraceptives, obesity, hormone replacement therapy, late menopause or early menarche, etc. Most of the endocrine disruptors are estrogenic contaminants those that interfere with the natural hormone signaling and actions. Many of these disruptors are industrial contaminants such as pesticides and plasticizers, others are natural phytoestrogens are supplemented from dietary nutrients and food (Table 1). These disruptors often block the hormone role or binding of the hormone to the receptors by mimicking the estrogen and other steroid hormones. In all the cases of endocrine disruptors, estrogen remains the gate-keepers of female reproductive health. Thus an increase in these disruptors that mimics or blocks the hormones leads to advancing puberty, less breast development and possible delaying in

menopause. Exogenous estrogen, diethylstilbestrol has effectively suppressed the lactation through which it leads to the breast disease and most of the time breast cancer [38].

### Therapies progressed for hormonal influenced cancers

Most of the female reproductive cancers are treated either by surgical methods or radiations. But these treatments are followed by adjuvant therapies of chemical inhibitors that mostly come under the category of hormone replacement therapy followed by drugs targeting a specific protein. Hormonal imbalance in female reproductive cancers can be treated with agonist or antagonist action of drugs for eg. Anti-estrogen that either block the estrogen from binding to the receptor and controls the cell proliferation or they binds to estrogen specific receptors and functions as estrogen. Some of the hormone replacement therapies are given in Table 2.

**Table 2. Targeted drugs and their action on female reproductive hormones in cancer**

Hormones	Targets	Drug	Action
Estrogen	Estrogen receptor (alpha or beta)	Tamoxifen	Selective estrogen receptor modulators (SERM) Blocks estrogen from binding to estrogen receptors
		Toremifene	
		Fulvestrant	Not an SERM but performs anti-estrogen activity
	Aromatase	Letrozole	These drugs stops the production and synthesis of estrogen by binding to the enzyme aromatase.
		Anastrozole	
Progesterone	Progesterone receptors	Exemestane	
		Megestrol acetate	Potent agonist that blocks the binding of progesterone to exert their effects
		Mifepristone	Partial agonist
		Aglepristone	Full Antagonist
		Ulipristal acetate	
		Asoprisnil	Selective progesterone receptor modulators (SPRM) that are in clinical trials
		Telapristone	

### CONCLUSION

Hormones are chemical messengers that exert their effect on the specific target cell or tissue by traveling in the blood stream. As these are involved both genomic and non-genomic signaling pathways it is necessary to regulate and control their concentration in serum and plasma. Increased or decreased concentration leads to improper function and action of these natural hormones. In terms of this disruption and hormonal imbalance are highly taken into consideration for women as they highly exposed to natural hormones and their role in women life starts from their first menstruation to menopause. Abnormal hormonal functions may cause an improper mural cycle, cyst development to cancer. In terms of cancer, most of the women related cancer are highly regulated through hormones. Deregulation in cell proliferation, differentiation and apoptosis allow the cells to incorporate mutated proto-oncogenes and tumor suppressor genes. The most common female reproductive hormones that are discussed here in this review are estrogen, progesterone, androstenedione, prolactin, and relaxin. These hormones they themselves or through their metabolites are showing effects in many cancers such as breast, ovary, endometrium, cervical and vaginal. Along with them they also stimulate other tumor related genes through which the cascade action of cancer progression is developed. This review also highlights the environmental factors and endocrine disruptors which could be risk factors for hormone-dependent cancers. Mostly the estrogenic effects of these disruptors helps in a blockade or mimicking the action of estrogen and other hormones by binding to their respective receptors and exerts their antagonistic or agonistic function in the target tissues. That resulting in the cause or development of cancers. Hence understanding the novel mechanisms of cancer progression helps in the development of novel therapeutics to control the metastatic and treatment of advanced cancer growth. Upon understanding the synthesis, role and mechanism of each hormone in normal as well as the diseased state gives a new knowledge and see through on the disease-related mechanisms. Hormone replacement therapy helps in various ways in controlling the overproduction of particular hormones and exposure to the target sites. But in terms of cancer, the continuous treatment of cancer and their adaptation to the particular drug has influenced the protein to modify their response to them sometimes they lead to resistance mechanisms that avoid the interaction of drugs with the particular binding site. Hence novel drugs should be designed upon understating the mechanism of resistance and role of mutations as well. Computational studies highly help in understanding the structural view of a protein with their mutation and their interaction with drugs.

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