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Mini Review

Hormonal Imbalance and Breast Cancer in Women

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Abstract

This article investigates the relation between hormonal changes and how it leads to breast cancer. Breast cancer is continuing to be one most of the most leading cause for the death of women especially worldwide. We referred many journals and articles that are recently published to get a clear picture of the indirect relation of hormonal changes and breast cancer. The hormonal changes lead to polycystic ovarian syndrome (PCOS), which is the main reason for infertility in the present generation. PCOS is considered to be a lifestyle disease, that can cause many hazardous health condition. This article clearly explains how obesity and PCOS are related and how it leads to breast cancer. The treatment strategies that are available now a days to cure breast cancers are also discussed. The drawbacks of the treatments and drugs are merely mentioned in the last section.

Keywords: Hormones; PCOS; Obesity; Breast Cancer; Hormone Receptors

Introduction

Cancer is a major public health problem worldwide and is the second leading cause of death world-wide in which breast cancer is the most common type of cancer in women [1,2]. According to the present statistics the breast cancer in women is increasing very fast in India. One of the reasons behind is the imbalance in female hormones which is a gift of our food habits and exercise free life. Obesity is the main contributing member for hormonal imbalance. Obesity can be associated with certain differences in the hormone of pituitary glands, which leads to many diseases like Growth hormone deficiency, hypothyroidism, hypogonadism and Cushing's disease. Adipose tissue can store energy and play the role of a mediator in hormone production and control substances synthesize and released of leptin and adiponectin. Further, obesity contributes a lot to polycystic ovarian syndrome whose main causative factor is hyperinsulinemia.

Hormones are compounds that wok as chemical messengers in the body. They can control many cells and tissues in various human body parts before reaching their site of action. The most important female sex hormones are estrogen and progesterone which are produced by the ovaries in premenopausal women and from fat in adipose tissues in both premenopausal and postmenopausal women. It supports the development of female sex characteristics and helps in the growth of muscles and centralbones. Progesterone is the prominent hormone that controls menstrual cycle and pregnancy. Higher level of estrogen and low level of progesterone leads to hormonal imbalance. Weight gain, mood swings, fatigue, skin problems and diminished sex drive are some of the symptoms of hormonal imbalance.

Breast cancer are of different types, in certain cases the sex hormones also promote the growth of some breast cancers, which are called hormone-sensitive (or hormone-dependent) breast cancers. There are certain proteins on the breast cancer cell surface

called receptors. In cancer cells hormone receptors (estrogen receptors, or ERs, and progesterone receptors, or PRs) that become activated when hormones bind to them. These types of activated cells proliferate very fast and leads to tumour. To confirm breast cancer only invasive techniques are now available in which doctors test samples of tumor tissue that have been removed by surgery. If the tumor cells contain estrogen receptors, the cancer is called estrogen receptor positive (ER positive), estrogen sensitive, or estrogen responsive. Similarly, if progesterone receptors are present on the surface of the tumor cells, the cancer is called progesterone receptor positive (PR or PgR positive). If any of the sex hormone receptors are present on the surface of tumor cells are called as hormone receptor positive (HR positive). Most ER-positive breast cancers are also PR positive. Breast cancer cells that have no ERs are called ER negative, and if both ER and PR are absent may be called HR negative. Approximately 70-80% of breast cancers in women are ER positive [3,4], about 90% of breast cancers in men are ER positive and about 80% are PgR positive [5].

Hormonal imbalance and obesity

It is well known that an increase in body weight and fat deposits in adipose tissue results in imbalance of of tes steroid levels in both premenopausal and postmenopausal women. Usually women with obesity have hyperandrogenism, even the clinical diagnosis of polycystic ovarian syndrome (PCOS)shows negative [6,7]. Radioimmunoassay (RAI) and liquid chromatography–mass spectrometry (LC/MS) have been widely used for measuring of serum testosterone in PCOS. Studies reveals that the earlier menarche time in girls have higher risk of developing obesity (8,7) and later in life they have a chance of developing other health issues such as diabetes, cardiovascular disease, breast cancer etc. [8-12]. Also, there are studies that reported that menarche at <12 years leads to higher androgens levels during adolescence. A recent study confirmed that each one year increase in menarcheal age, the chance of being obese decreased by 22% [11].

Estrogens play an important role in energy storage and usage, weight management, fat distribution, and human metabolism. In healthy women during the reproductive period, estrogens are mainly produced in the ovaries under strict control of gonadotropins from the pituitary gland. They can also be produced in the adipose tissues via aromatization of androgens. Aromatization is the process of converting a nonaromatic ring into an aromatic ring catalysed by aromatase enzyme. Estrogens contain an benzene ring which has electron delocalisation and hence it is aromatic. The estrogen produced through aromatisation has a role in men and post-menopausal women and increases in its proportion to the total body adiposity [13,14]. Metabolic effects of estrogens are controlled by estrogen receptor (ER) Alpha, whereas most gynaecologic actions are by ER Beta. ER Alpha is currently attracting the researchers. Estrogens have a positive effect in maintaining glucose balance in women. It is an insulin sensitizer acting at multiple levels, including skeletal muscle, liver and adipocytes [15,16]. Even estrogens can control the immune system. This can reduce the inflammation in body and thus affects the insulin amount in human body [17,18]. Islets of Langerhans in pancreas have ER which can control the function of beta cells [19]. Estrogen deficiency leads to low metabolic function which paves way for obesity and type 2 diabetes. Type 2 diabetes is condition in which the body uses sugar (glucose) as a source of energy. This long-term circulation of too much sugar in blood stream, which results in high blood sugar levels and leads to the mal functioning of nervous, immune, excretory and circulatory systems. Visceral obesity is boosted in lower estrogen levels, as seen in menopause. These changes in body fat composition can be prevented by estrogens replacement [20]. Also, estrogen treatment in transsexuals significantly increases fat deposition in all adipose tissues leading to little effect on the visceral obesity [21].

Obesity and polycystic ovarian syndrome

Polycystic ovarian syndrome (PCOS) is a direct result of hyperandrogenism which is contributed by obesity. Hence, this disorder has been studied widely when the relation between sex hormones and obesity is the problem. It affects approximately 8-12% of women in reproductive age [22]. About two thirds of women with PCOS are obese and 60.0-80.0% of them have insulin resistance (IR) [23]. Women with PCOS is characterised by increased fat deposit in adipose tissue [24,25]. This increased visceral obesity leads to insulin resistance in women with PCOS, which can lead to diabetes, heart attacks, hypertension and other serios disorders [22]. Interestingly, in PCOS, the ovaries are highly prone to stimulation than other organs due to the presence of androgens [26]. Recent studies reveal certain common symptoms in women suffering from PCOS and women with the metabolic syndrome. Even though these are different entities, hyperandrogenism (higher level of androgens) in both cases makes these similarities [27].

Irregular ovulation and menstrual discomforts like heavy bleeding, bleeding persist for many days etc are major features of PCOS; these are in part due to ovarian hyperandrogenism, hyperinsulinemia due to decrease in cellular ability to respond to insulin signalling, leads to all metabolic complications of PCOS and it changes the function of pancreas which can disrupt follicle growth [22]. Hyperinsulinemia retards the action of hepatic sex hormone-binding globulin leading to subsequent increase in free androgens levels.

In summary, obesity is direct result of PCOS. Hyperinsulinemia is the main causative agent for the development of PCOS and hyperestrogenism. The women with PCOS can improve fertility by weight loss or by using insulin sensitizing agents like metformin which reduces insulin levels, but not live births [28,29]. Metformin is being widely used to improve the chances of pregnancy but no evidence that it can improves live birth rates, whether it is used alone or in combination with clomiphene [30], this is the main drawback of metformin that it cannot improve reproduction capacity in women with PCOS [31]. Letrozole, an aromatase inhibitor, is used as a substitute for clomiphene, a selective estrogen receptor modulator that can lead to the production of healthy eggs in women with PCOS. Treatments with drugs like metformin, troglitazone or d-chiro-inositol have failed in case of improving live birth rates, studies are going on to find newer drugs to treat type 2 diabetes and to improve the live birth rate [31].

Is there a relation between PCOS and breast cancer?

The relation between PCOS and cancer is a great matter of confusion in medical field till 2020. Recently it is reported that PCOS was one of the etiological factors of ER-positive breast cancer [32]. The studies conducted by Moradi., *et al*. confirms the association between fibrocystic breast changes and PCOS [33]. The relation between PCOS and fibrocystic breast changes may be due to several reasons. As we discussed earlier the side effects of hyperandrogenism in PCOS is high, which inhibits progesterone activity and resulting in high proliferation of mammary cells, breast enlargement, and fibrocystic breast formation [34- 37]. The next result of PCOS is the conversion of androgens to estrogen and the stimulatory effects of estrogen on the growth and division of the mammary epithelium [38-41]. The lack or irregularity of ovulation is a direct effect of PCOS. The case study conducted by Gumus., *et al*. showed that out of 53 PCOS cases, 21 had fibrocystic breast change characteristics (39.6%) while out of 40 healthy controls, not suffering from PCOS, only 4 had fibrocystic breast changes (12.5%) and this difference between two groups was statistically significant [42]. In another study conducted by D'Amelio., *et al*. examined the association between PCOS and fibrocystic breast changes. There are two set of people in this study, one with PCOS and other health control group without PCOS. The prevalence of fibrocystic breast changes in first group and second groups were 92.0% and 7.0%, respectively, which showed a significant relationship between these two diseases [43].

Many studies now a days reveals the truth that PCOS is a good contributing member of breast cancer in women. As we know the hormonal imbalance is the main reason for PCOS. In short, the lack of balance in hormones quality and quantity is a silent factor that promotes the development of breast cancer.

PCOS medications that may influence cancer risk

Oral contraceptives

For women who don't want a pregnancy and those having menstrual irregularities due to PCOS oral contraceptives are the first stage of treatments [44]. The effect of these combined oral contraceptives is the imbalance of hormones in the body of woman which can lead to cancer. The symptoms nay remain buried for years but may come to action after some years [45]. The risk of breast cancer due to oral contraceptives is less pronounced which indicates it's usage las a very low side-effects [46].

Metformin

Metformin is prescribed as a medicine for women with PCOS to treat menstrual irregularities and for type II diabetes by decreasing insulin resistance. Studies confirms that metformin use may be protective against various forms of cancer [47]. However, only a few studies have been conducted to find the contribution of metformin on endometrial, breast, and ovarian cancer.

Breast cancer is one of the most studied type of cancer among three cancers that are influenced by metformin. Researchers are legitimate about increased breast cancer chances in women using Metformin [48]. The use of Metformin contribute a good part for the development of other cancers like endometrial and ovarian cancers [49-52].

Treatments for breast cancer

Local therapy for invasive breast cancer: breast-conserving therapy (Lumpectomy) and mastectomy

Breast-conserving therapy (BCT) and mastectomy are both well-established local therapies for invasive breast cancer. Breast-conserving therapy (BCT) refers to breast-conserving surgery (BCS; ie, lumpectomy) is done by using radiation therapy (RT) to eradicate any microscopic residual disease. It is generally used for patients with early breast cancer. In this treatment method only the affected part of the breast (the tumor lump and some tissues around the lump) is removed. In this case the chances of reoccurrence are very high. Physical examination, mammography, and diagnostic ultrasound are the imaging modalities in standard use to select patients for BCT.

Mastectomy is the surgical procedure to remove entire breast tissues to prevent further spreading of the cancer. Simple mastectomy keeps some lymph nodes as much but in modified radical mastectomy entire breast along with the lymph nodes are removed.

Mammography, physical examination, and ultrasound scanning are the imaging techniques widely used for the confirmation of cancer in patients under BCT. MRI is more sensitive than mammography or ultrasound in detecting other diseases in patients before using invasive techniques or operation [53]. It was hoped that MRI would help in the early detection of lumpectomy and decreases then rates of reoperation.

Chemotherapy

The treatment of cancer with drugs are collectively known as chemotherapy. This type of treatment is generally opted for patients having high risk. The measurement of risk is based on the number of lymph nodes affected and the size of tumor as compared to the breast size of the patient. The most commonly used drugs are Anthracycline and a Taxane. In certain countries like USA Paclitaxel, Doxorubicin, Docetaxel etc are also used. The later set of drugs are more expensive than the former ones [54-56]. Generally, the patients having Node positive breast cancer is highly recommended for chemotherapy. A patient detected with Node positive breast cancer means the cancer has been spread to the lymph nodes in underarms. The Node positive breast cancer indicates that the disease proceeded to stage 2. The Node positive breast cancer are metastatic ie they can move to any part of the body. In most of the cases it generally attacks the nervous system through spinal cord. Now a days the overall 5-year survival rate of Node positive breast cancer has been increased to 91.83% in India but it is 96.17% for Node negative breast cancer. The disease-free survival rates are 84.0% and 92.0% respectively [57].

Biological targeted therapies

There are a large number of receptors on the surface of the tumor cells. This type or receptor targeted therapies are generally called as “Biological targeted therapies”. Some of the receptors are folate receptors (FR), epidermal growth factor receptor (EGFR), Hyaluronic acid receptors, Hormone receptors (HR) etc. The HR positive cancer means it may have Estrogen receptor (ER) or Progestrone receptor (PR) and both. Hormonal therapy is generally opted for this type of cancers. The receptor targeted therapy is greatly used for HER2 (Human Epidermal Growth Factor Receptor 2) positive cancers. The presence of HER2 targeted agents has increased the chance of recovering in HER2 positive breast cancer patients. The starting of treatments in cancer patients by chemotherapy alone or by chemotherapy and drug trastuzumab (HER2 receptor targeted monoclonal antibody), demonstrated nearly 50% reduction in reoccurrence of the cancer [58-62].

Endocrine therapy/Hormonal therapy

Endocrine therapy is the most pronounced treatment methods for patients with HR positive tumor. This therapy retards or completely stops the proliferation of hormone-sensitive tumors by blocking the certain gland’s ability to produce hormones or by interfering with effects of hormones on cellular division of breast cancer cells. Cancer cells having no hormone receptors do not respond to hormone therapy. The concept of hormone treatment for breast cancer should not be confused with menopausal hormone therapy (MHT)—treatment with estrogen alone or in combination with progesterone that helps to overcome the adverse symptoms of menopause. These two types of therapy produce opposite effects: hormone therapy for breast cancer retards/stops the growth of HR-positive breast cancer, whereas MHT can be a reason for the development of HR-positive breast cancer. Due to the above reasons when a woman taking MHT is confirmed of having HR-positive breast cancer she is usually prescribed to stop that therapy.

The main drawback of this therapy is the side effects of the drugs used. The most commonly used drugs are Tamoxifen, Raloxifene, Aromatase inhibitors, Fulvestrant etc. The main side effects include risk of cataracts, uterine sarcoma, blood clots especially in the lungs and legs, stroke, and endometrial cancer it leads to weakening of bones in premenopausal women, but no increased risk of fracture, mood swings, depression, and loss of libido.

Conclusions

Nowadays our routines and food habits are making our body a good host for many fatal diseases. The hormonal imbalance is the main issues faced by our women. This type of mal functioning of hormone are contributing a lot in making their life miserable. Obesity is the main reason for hormonal imbalance leading to PCOS. It's very difficult for a woman with PCOS to reduce even 500 gm from their total body weight. From the above discussions it is clear that the hormonal imbalance is the silent reason for the most deadly breast cancer. Eventhough there are good treatment options for cancer at present, no one can promise 100% survival or 0% recurrence. But medical science has been developed so much to promise good survival in the early detection. That is a great achievement. In short, by altering our food habits adding some exercises to our daily plan can save us from this deadly demon: CANCER.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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