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Relation between Leptin and Estrogen in Breast Cancer: A Literature Review.

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ABSTRACT

Breast Cancer is the most prevalent cause of cancer related death in women. According to estrogen and leptin role in hormone dependent breast cancer and their correlation in this cancer, we decided to review the published articles to gather the present information and discuss about it. In these articles express there is a direct and positive correlation between progesterone and estrogen with leptin expression. Also they demonstrate that leptin and estrogen can stimulate the other one by different mechanisms in estrogen receptor-α positive (ER-α positive) breast cancerous cells.

Keywords: Leptin, Estrogen, Breast Cancer

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INTRODUCTION

Breast cancer is the most current cause of cancer related death among the women. This disease is diagnosed in 1/4 million of women around the world and cause more than 450000 death each year [1]. Epidemiologic studies show correlation between obesity and increasing risk of some cancers. There are convincing proofs which report the relation of breast cancer and obesity in postmenopausal women [2]. In addition immoderate body mass index (BMI) can significantly increase the risk of inflammatory breast cancer; the mortalest type of breast cancer in pre and postmenopausal women with obesity in upper part of body [3]. One of the adipose-derived hormones which is coded via obesity gene (Ob) is leptin and deficiency of this hormone can cause obesity [1].

Leptin acts via leptin membrane receptor (ObR) and ObR's expression increase in breast cancer. In addition, studies demonstrate it could be stimulate the cell proliferation, angiogenesis, migration and invasion in different cells [1]. New information signifies that leptin can cause carcinogenesis probably and it is notable that leptin and its receptor (ObR) are expressed more in epithelium of cancerous breast than normal breast epithelium. A lot of proofs show correlation between obesity in postmenopausal (which is measured by BMI) and increasing risk of hormone dependent cancer, estrogen receptor-α positive and progesterone receptor positive (ER-α positive and PR positive). Obesity's mechanism that can supply hormone dependent breast cancer is unknown but probably some ingredients contribute in increasing exposition of breast cancer epithelial cells to adipose local estrogen and in low modulation of globulin dependent sex hormones which occur in women with high WHR(waist-to-hip ratio) [3].

Estrogens play an important role in breast cancer; they possibly act via stimulating cell proliferation and oxidative metabolism which transact indirectly by different cytochrome P450 enzymes like CYP1A1 and CYP1B1. On the other hand, as regards to present proofs we can suggest intermediation role of estrogen in leptin gene expression in adipose tissue[4].

METHODOLOGY

In this review research which accomplish to study correlation between leptin and estrogen in breast cancer, we use last 15 years published articles recorded in pub med database. We use ''estrogen'', ''leptin'' and ''breast cancer'' key words to search these articles.

Literature review

In a study conducted by Khanal et al. concerning to the effect of leptin on CYP1B1 expression and the mechanism of its action on breast cancer cells, findings indicate leptin could be increase CYP1B1 expression in ER-α positive cells like MCF-7 but there is no effect on ER-α negative cells like MDA-MB-231 cell line. Furthermore, mechanism of leptin's effect on stimulating CYP1B1 expression with mediation of ER-α pathway via direct activator ligand was determined. They deduce these results by this research:

1. Leptin stimulates CYP1B1 expression in ER-α positive cells like MCF-7.
2. Leptin cause serine residues phosphorylation in MCF-7 and finally stimulates functional activity of ER-α.
3. Leptin stimulates ER-α phosphorylation in MCF-7 cell line via Akt and EPK pathway [4].

Fusco et al. demonstrate mutual functional encounter between leptin receptor and estrogen receptor signaling pathway cause promotion breast cancer [5]. In addition, Miyoshi mentioned estrogen cause increased regulation of leptin and its receptor expression in MCF-7 cell lines [6].

In another study which carried out by O'Neil et al. the mechanism of estradiol action to activate the leptin promoter in different types of cells were surveyed. They demonstrate estrogen's ability to activate leptin promoter through ER-α in JEG-3 breast cancer cells. They suggest leptin synthesis regulation may be associated with functional role of estrogen. In contrast, ER-β activity in leptin promoter inhibited by E2 slightly; although it is

stimulated by antiestrogens. It suggests that regulation of tissue synthesis leptin depends on present estrogen levels in target tissues. This study proves estrogen molecular activation mechanism in activating leptin promoter and many other proofs to demonstrate normal leptin synthesis regulation mechanisms in tissue [7].

In their investigation Marttunen et al. examined antiestrogen effects on circulating leptin levels. In this study 30 women suffering from breast cancer treated with tamoxifen or toremifene leptin concentration was measured in three phase: before treatment, 6 and 12 months after treatment. They express adipose cells have estrogen receptor that may play role in leptin synthesis control. According to association of plasma leptin and estrogen concentration and unsuccessful estrogen replacement therapy in women with high levels of circulating leptin as well as observing increasing effect of estrogens on leptin that isn't correlated with body mass changes, can expect antiestrogens cause estrogen receptor stimulation in adipose cells and regulating leptin secretion [8].

In Garofalo et al. study which reviews correlation of leptin and cancer development, direct and positive correlation between leptin and increasing ER, PR and risk of breast cancer was observed. In this research ER-α positive cells like MCF-7 and T47D express more ObR than ER-α negative cells like MDA-MB-234 and MDA-MB-435. ER-α positive cell lines like MCF-7, T47D and ZR75-1 cause stimulating DNA synthesis and cell growth via multiple hormone cascade pathway including PKC-α, ERK1/2 and JAJ/STAT path. It should be noted leptin in T47D cell lines not only cause cell growth but also cellular transformation (anchorage-independent growth) which is breast cancer cells exclusive. Special correlation between leptin and ER-α is also remarkable. Last reports demonstrate ER-α and ObR expression in both normal and malignant breast tissues. In addition of these detections leptin can modulate estrogen production and ER-α activation [3].

In another study achieved by Garofalo to investigate expression of leptin and its receptor in breast cancerous epithelium of primary and metastatic patients and healthy individual and also development of leptin or ObR express via obesity related stimulators like insulin, IGF-I, estradiol or hypoxia term indicate leptin's intervention in brest cancer via signaling estrogen synthesis. Especially in MCF-7 cells, leptin cause stimulating aromatase gene expression and activation and increasing estrogen synthesis eventually. Leptin also develop ER-α dependent transcription by decreasing ubiquitination in ER-α, especially in ICI182/780 antiestrogen existence. In addition, studies show leptin's modulation by ER-α transaction via kinase 1/2 extracellular signaling pathway. The mechanism of leptin/ObR overregulation in breast epithelium is unknown but hormonal factors like insulin, IGF-I and estrogen affect leptin synthesis in other cellular systems [9].

In Slukowska et al. study leptin can increase ER-α stimulating in MCF-7 and Hela cells via MAPK (mitogen activated protein kinase). It seems antiestrogens compete leptin for regulating ER- activation. Therefore, increasing serum leptin levels can be responsible for overcoming antiprolifrative effects of antiestrogens [10].

CONCLUSION

Nowadays breast cancer is one of the most current cause of cancer related death in the world and the risk of breast cancer developing, increase in obese postmenopausal women [11]. According to leptin production in adipose tissue, we can attribute obesity risk in breast cancer to leptin expression level. On the other hand, as regards of estrogen role in breast cancer it could be concluded a relationship between leptin and estrogen in patients with breast cancer. According to Khanal study leptin can stimulate ER-α phosphorylation and activation via EPK and Akt pathway in MCF-7 cells. Some researches demonstrate estrogen ability for activating leptin promoter in JEG-3 breast cancer cells Via ER-α [4]. In Garofalo' s investigation mentioned 1. Positive and direct correlation between leptin and increasing ER, PR level and risk of breast cancer. 2. Leptin can increase expression and activation of aromatase potentially and cause est synthesis signaling 3. Hormonal factors like insulin, IGF- I and estrogen effect on leptin synthesis 4. Leptin can stimulate DNA synthesis and cell growth in ER-α positive via multiple hormone cascade pathway like JAJ/STAT , ERK 1/2 and PKC- α [3, 9].

Sulkowslea et al. Express leptin can increase ER stimulation via MAPK. Therefore, they suggest theory of leptin and antiestrogens competition in regulation of ER activation. Thus, leptin inhibits antiestrogen therapeutic effects [10].

According to investigated researches in this study, leptin and estrogen have association with each other and increasing each of them can increase the other one by different mechanisms. As a result, leptin expression level in hormone dependent breast cancer and hormone therapy can be important.

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