



REVIEW ARTICLE

Obesity as potential breast cancer risk factor for postmenopausal women

Swati Sucharita Mohanty*, Prafulla Kumar Mohanty

Cytogenetics Laboratory, P.G. Department of Zoology, Utkal University, Bhubaneswar, 751004, Odisha, India

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Abstract Breast cancer is the second highest prevalent cancer globally after lung cancer with 2.09 million cases during 2018. Adults about 1.9 billion were overweight and over 650 million out of these were obese during 2016. There is a significant relationship between breast cancer risk and obesity. Premature menopause and premenopausal obesity diminish the risk whereas postmenopausal obesity amplifies the risk, because adipose tissue acts as the major reservoir for estrogen biosynthesis after menopause. Lofty estrogen levels in serum along with enhanced peripheral site production of estrogen have been viewed as major reasons of developing breast cancer in overweight postmenopausal women. This review explains body fat as a peripheral site for estrogen biosynthesis, estrogen exposure affecting body fat distribution, and the mechanism of estrogen production from body fats.

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Introduction

Approximately 9.6 million people decimated due to cancer worldwide in 2018, rendering it as the second-most cause of mortality; while, breast cancer is next to lung cancer with recoded 2.09 million new cases and is regarded as the fifth highest common cause of cancer death for 627,000 deaths in 2018.¹ In India, 162,468 new cases of breast cancer and 87,090 deaths have been recorded in 2018.^{2,3} Epidemiological studies during 2016 reveal that adults about 1.9 billion were overweight and over 650 million out of these were obese.⁴ Further, 40% of females aged 18 years and above were overweight and out of these adults females 15%

Abbreviations: BMI, body mass index; ER, estrogen receptor; E2, estradiol; MAPK, mitogen-activated protein kinases; GPER1, G protein-coupled estrogen receptor 1; GPR30, G protein-coupled receptor 30; IL-6, interleukin-6; TNF α , tumor necrosis factor- α ; IRS-1, insulin receptor substrate-1.

* Corresponding author.

E-mail addresses: swatimohanty16@gmail.com (S.S. Mohanty), prafulla.mohanty3@gmail.com (P.K. Mohanty).

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were obese according to WHO during 2016.⁴ In India during 2015 29% of females aged 30 years or above were overweight, which is expected to increase over the next ten years.⁵ Obesity and/or overweight, is calculated in form of body mass index (BMI) [$BMI = \text{weight (kg)}/\text{height (m}^2\text{)}$] or may be estimated by the distribution of fat in the body, is a known risk factor for breast cancer in postmenopausal women, which is associated with the synthesis of estrogen from fat tissues.⁶ Peripheral or central distributions of fat are the two most commonly used and clinically appropriate classifications to assess the degree of obesity.⁷

Recent studies suggest a positive association between BMI and breast cancer risk. According to a meta-analysis by Liu et al there is a weak positive association showing about 5 kg/m² raise in BMI requited about 2% increase in breast cancer risk; whereas, higher BMI in premenopausal female have a protective effect for breast cancer risk.⁸ Also Iyengar et al showed that excess adiposity in postmenopausal females is associated with increase in risk for breast cancer especially hormone dependent estrogen/progesterone receptor positive (ER/PR + ve) cancer.⁹ Despite the fact that obesity in premenopausal women seems to be linked with decline in chance of developing breast cancer, this could be due to the combination of anovulatory cycles and lower progesterone levels late in the menstrual cycle,⁶ but only applicable to younger obese women. Obesity is not merely a risk factor for breast cancer; it is equally a potent prognostic factor which predicts upshots of the disease.⁷ Obese breast cancer women have a high possibility to develop larger tumors, well progress stage at the time of first clinical examination, high rate of metastasis and may generate resistance to hormone therapy.^{10–12} Since clinical evidences show that obese breast cancer patients who are treated with chemotherapy or aromatase inhibitors have a chance of recurrence and an abridge effect to clinical intervention in contrast to slim women.^{12–15}

Overweight and obesity are considered to have a protective effect of for the breast cancer in premenopausal, except aside from women with a family background of this ailment; so body fat could be a good improved predictor of breast cancer risk in postmenopausal women over either BMI or body weight, body fat distribution could also influence the risk of breast cancer.¹⁶ Information about adipose tissue has expanded significantly over the past few years. Although adipose tissue has always been described as an inert tissue use to store lipids; however, at present it is identified like a true organ possessing both metabolic and endocrine functions exuding a variety of components into the bloodstream to communicate with other organs and tissues.^{12,17–19} Those components, altogether known as adipokines, are essential in causing a group of physiological responses namely the metabolism of glucose and lipids, homeostasis, angiogenesis, inflammation and satiety.^{12,20} Deregulation of hormonal role and uncontrolled expression of adipokines in the adipose tissue, cause overweight or obese state, finally connecting obesity with risk for breast cancer.^{12,21–23} Increased adiposity induces the growth and advancement of breast cancer for postmenopausal women through production of more estrogen, which cause more estrogen exposure to breast tissue;

estrogen exposure is the major cause of breast carcinogenesis.^{12,24}

A huge quantum of data on obesity as a risk factor for breast cancer in postmenopausal are on record; such as excess body fat is directly proportional to increase in risk of breast cancer for postmenopausal women.²⁵ Similarly, obesity increments the risk for postmenopausal breast cancer; thereby helps in diagnosis, treatment and prognosis of breast cancer.⁷ There are evidences that estrogen has a link with both obesity and risk for breast cancer.¹⁶ Review about appropriate methods to evaluate obesity and its link to breast cancer risk and prognosis,²⁶ also how obesity influences the hormone dependent risks of breast have been cited.¹² This review explains body fat as a peripheral site for estrogen synthesis; body fat distribution is affected by estrogen exposure, and the mechanism of estrogen production from body fats.

Estrogen exposure and excess body weight

Sex hormones control body adipocyte differentiation and fat distribution, so both estrogen and testosterone influence adipocyte physiology in a different manner (Fig. 1). Estrogen and estrogen receptors manage a range of pathways for lipid and glucose metabolism. The fat distribution pattern in the female due to estrogen is typically at breasts, thighs and buttocks, which gives a more feminizing effect to female.¹⁶ During the reproductive years to supply strength for eventual pregnancy and lactation, women get extra fat deposition in the breasts, thighs, pelvis, and buttocks.^{16,27} A notable rise in estradiol, estrone and free estradiol for postmenopausal women are linked with increased BMI, this can be controlled by regular physical activity which lowers estrogen serum levels.

It is a known fact that increased exposure to endogenous estrogen all the way through a women's life, primarily owing to their reproductive record, has an escalating risk of developing breast cancer influenced by ovarian sex hormone.^{25,28} Prolonged exposure to estrogen such as menarche at a young age or delayed menopause may boost the risk of breast cancer.²⁵ This association between ovarian hormones and breast carcinogenesis has been documented many times by outlining elevated serum levels of sex hormone in women with breast cancer in contrast to those in control cases.^{29–32} Low serum availability of sex hormone binding globulin in postmenopausal obese women cause higher serum availability of bio-available estrogen than in postmenopausal women who are thin. So this suggests, for postmenopausal women, there is an affirmative connection between obesity and amplification of breast cancer risk.²⁵ Likewise, premenopausal women who are obese, are liable to have lengthy menstrual and increased anovulatory cycles than premenopausal women who are lean, as a result, there is less total exposure to estrogen and a reduced breast cancer risk.^{6,25}

Majority of breast cancers about more than 75% are hormone-dependent breast tumors expressing estrogen receptor (ER), which grows in response to estrogen hormone.³³ The estrogen estradiol (E2), has an essential status

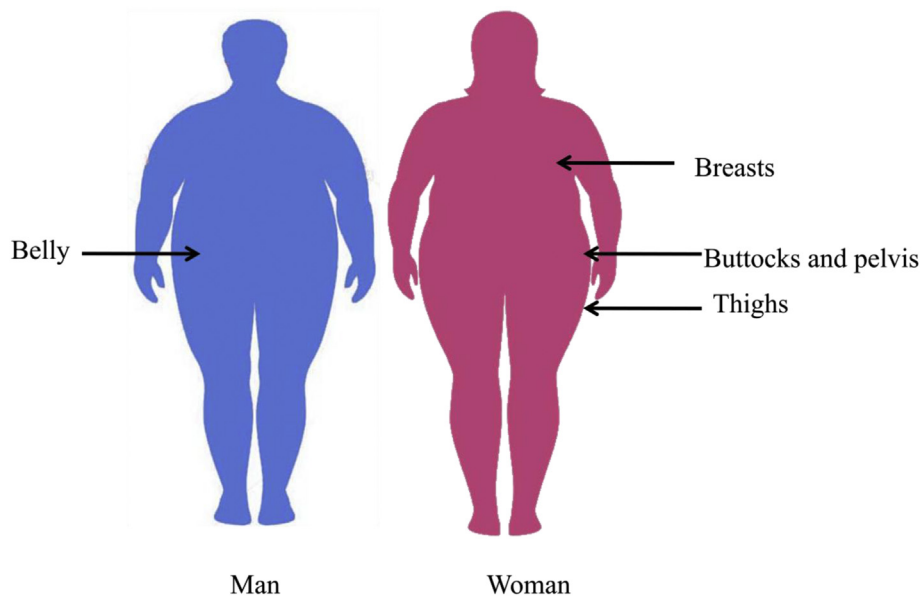


Figure 1 Fat distribution pattern in male and female.

in normal and reproduction physiology, which is necessary for the advancement and growth of standard breast epithelium by organizing postnatal epithelial cell growth and ductal ontogenesis.³³ However, large quanta of clinical data have also shown the elementary responsibility of estradiol and its receptors as the pathological cause and development of breast cancer.^{34,35} E2-activated ER controls carcinogenesis of breast by using intricate signaling pathways that manages multiple cellular responsibilities, namely angiogenesis, migration, growth and apoptosis.^{36–38} ER is principally a protein which acts like a ligand dependent transcription factor. Usually, the E2/ER complexes after fusion and co-regulator enlistment, bind easily to estrogen responding space in the promoter area of targeted genes.^{36,39} Thus, this regulates transcription of estrogen responding genes that are vital for different pathological and physiological actions, including tumor progression and carcinogenesis.

ERs are present in the cytoplasm or on the membrane cause rapid activation of mitogen-activated protein kinases (MAPK) pathway; as a result, it alters a range of cellular functions.⁴⁰ Another accepted membrane estrogen receptor called G protein-coupled estrogen receptor 1 (GPER1), which is also known as G protein-coupled receptor 30 (GPR30), is lately presumed to amplify physiological and carcinogenic property of estrogen hormone.^{41,42} This is why endocrine therapy is the most commonly used and adjuvant therapy is very efficient for ER positive breast cancers, as it relies on estrogen repression and jamming the hormone communication with its receptor.^{43,44} Tamoxifen, as a selective estrogen receptor modulator, has been used for almost three decades to deal with hormone dependent breast cancer and it has greatly enhanced the survival rate of initial stage breast cancer in person by reducing recurrence rate.⁴⁵ Over the years, aromatase inhibitors have been established as more efficient treatment, because of fewer side effects and now considered as primary defense therapy in postmenopausal women.^{44,46}

Body fat acts as key source of estrogen biosynthesis

The estrogen biosynthesis is different in premenopausal and postmenopausal women. In premenopausal women estrogen is generally synthesized by the ovaries, on the other hand, ovarian biosynthesis is replenished by secondary sites (Fig. 1) synthesis in postmenopausal women, in whom body fat acts as key source of estrogen biosynthesis. Aromatase is the primary arbitrator of postmenopausal estrogen biosynthesis, which is an enzyme found in adipose tissues of the breast as well as cancer affected tissues. Aromatase can also convert androgens, synthesized by the ovary and the adrenal cortex of postmenopausal women, into estrogen.¹⁶ This leads to high estrogen production level in cancerous breast tissue; that is, almost ten times higher in comparison to the level in circulation. Moreover, interleukin-6 (IL-6) and tumor necrosis factor- α (TNF α) are both generated copiously by adipocytes (fat cells) and they can perform in either paracrine or autocrine way to amplify generation of aromatase, this will ultimately increase synthesis and high bioavailability of estrogen hormone. Finally, estrogen controls the insulin receptor substrate-1 (IRS-1) in mammary tissue,⁴⁷ which persuades DNA impair due to free radical, increases genetic imbalance which may cause mutations, and inhibits both apoptosis and DNA repair.^{48–50} Peripheral biosynthesis of estrogen in postmenopausal women is controlled by a large amount of distinctive aromatase inhibitors and utilization of the aromatase inhibitors are being appraised.¹⁶

Mechanism of estrogen production in adipose tissue by aromatase

Estrogen is synthesized from androgen by aromatase, which is contained in the endoplasmic reticulum.⁵¹ Biosynthesis of estrogen varies greatly among premenopausal and

postmenopausal women, for premenopausal women granulosa cells of the ovary are the sites where estrogen is produced abundantly with every menstrual cycle, while other organs namely: the vascular aortic smooth muscle, adipose tissue, bone, endothelium or the brain also produce low level of estrogen.^{51–54} Menopause is a stage when ovarian functions terminate ultimately and the main source of estrogen becomes extra-gonadal sites.⁵⁵ Consequently, the major site of estrogen biosynthesis in postmenopausal obese women is believed to be due to excess adipose tissue (Fig. 1), which causes the circulating estrogen concentration to increase many fold.⁵⁶

The main components of adipose tissue are fibroblasts, pre-adipocytes, mature adipocytes, nerve cells, immune cells and endothelial cells for which it is classified as a highly heterogeneous tissue.⁵⁷ The main source of aromatase expression is the pre-adipocytes,⁵⁸ which controls estrogen biosynthesis in the breast and may result in breast carcinogenesis.⁵⁹ Aromatase expressed in mammary pre-adipocytes are more potent in the development of carcinogenesis than those aromatase expressed elsewhere in body because it is closer to the breast epithelial cells.⁶⁰ Aromatase expression along with biosynthesis of estrogen has also been found in breast cancer tissue, which leads to expansion in answer to autocrine signals.⁶¹

Cholesterol's major source in body are adipose tissue and all steroid hormones can be derived from it. The three major estrogens with potential estrogenic hormonal powers are estrone (E1), estradiol (E2), and estriol (E3). Estetrol (E4) is another type of estrogen, produced only during pregnancy.⁶² The predominant circulating estrogen during reproductive years is estradiol, during menopause is estrone and during pregnancy is estriol. However, estradiol is the most potent estrogen. Usually estrogens hormones are produced by ovaries when stimulated by Follicle stimulating hormone, which is control by gonadotropin-releasing hormone. After menopause the biosynthesis of estrogen get shifted to extragonadal tissues such as adipose tissue (Fig. 2).^{63,64}

Biosynthesis of estrogen requires oxidative enzymes, which can be found in both endoplasmic reticulum and

mitochondria. First cholesterol is converted into to pregnenolone by an enzyme called CYP11A1. Pregnenolone is a direct progenitor for the synthesis of different steroid hormones, but is not a hormone itself. Pregnenolone change to progesterone or 17-hydroxy pregnenolone by two different enzymes namely 3 beta-hydroxysteroid dehydrogenase and 17 alpha-hydroxylase/17, 20 lyase respectively. Subsequently 17-hydroxy pregnenolone changes to androstenedione through different steps. Androstenedione changed into estrone either right away, or into testosterone and then to estradiol by the enzyme aromatase (Fig. 3).

To describe signaling pathway in short: a number of different promoters control the aromatase transcript expression in an elaborate method and tissue-specific manner.⁵³ Till date, in human ten different promoters have been recognized, which includes promoters such as I.5 in fetal tissues, skin and bone, I.4 in adipose tissue, I.1, I.2 and I.2a in placenta, I.7 in endothelial cells, I.f in brain, I.6 in bone, PII in gonads and adipose tissue and I.3 in adipose tissue.^{60,65,66} Each promoter results in different spliced forms of mRNA having matching coding areas but diverse initial untranslated exons upon activation. Thus, aromatase expression is alike in all areas in spite of different promoter used.⁶⁷

Weak promoter such as PI.4 is accountable when it comes to keep expression at low levels for aromatase and as a result biosynthesis at low levels of estrogen occurs in adipose tissue of healthy mammary gland, whereas powerful promoters like PII and PI.3 remains dormant.⁶⁸ Glucocorticoids namely: tumor necrosis factor α (TNF α) and class I cytokines (interleukin-6 and 11) control Promoter PI.4 in normal breast tissue^{69,70}; however, in obesity associated breast cancer, powerful promoters II and I.3 are triggered, causing amplification of aromatase expression.⁷¹

Weight reduction to reduce risk of cancer

Avoiding weight gain is the main way to prevent from any type of serious disease in this modern times, weight can be controlled by increasing physical activity with decrease in

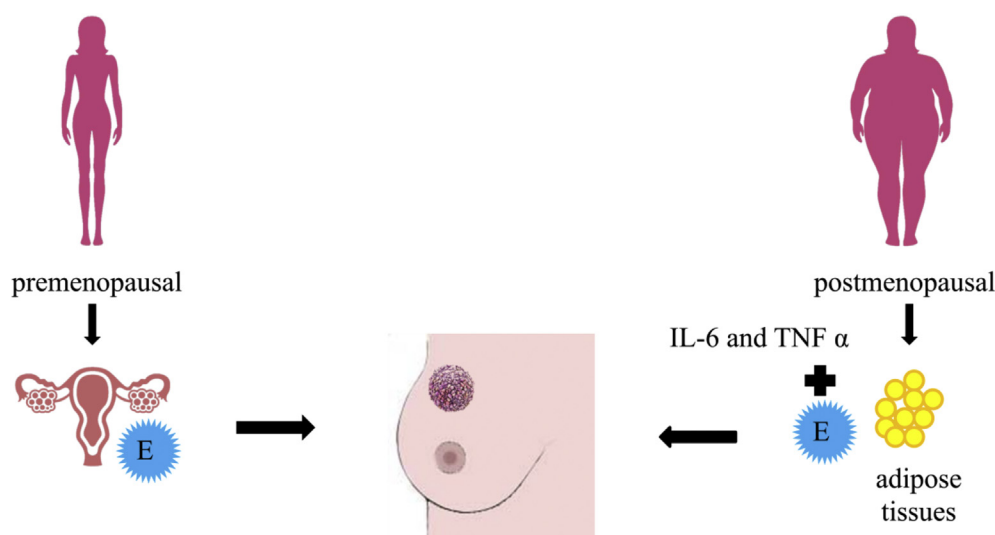


Figure 2 Sites of estrogen synthesis in premenopausal and postmenopausal females.

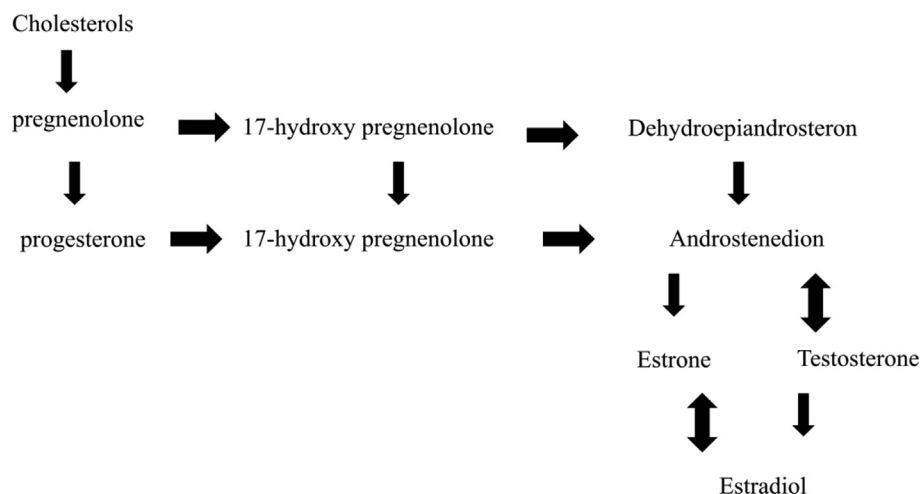


Figure 3 Biosynthesis of estrogen.

energy intake especially high sugar intake.²⁵ Moreover, benefits from physical activity are above and beyond just weight control. Exercise or at least walk for 30 min per day and maintaining a calorie chat per day is useful. Obese person should try to change their sedentary lifestyle. Weight reduction as a result of either gastric bypass surgery or caloric restriction has proven to result in a decrease of circulating estrogen.^{16,72} Since hormone positive breast tumors are influenced by estrogen cues for development in postmenopausal women, it is obvious that weight reduction and simultaneous decrease in estrogen level should cause decline in breast tumor development.^{16,73}

Conclusions

Obese postmenopausal women are at a high risk of developing hormone-sensitive tumors, because of high level of estrogen in serum as well as peripheral site generation of this hormone. Furthermore, aromatase found within adipose tissue could also sway breast carcinogenesis by affecting together serum and peripheral site generated levels of sex hormones. Considering that obesity may reduce the efficiency of endocrine therapy, it is possible that weight loss will increase the efficiency of these therapies in breast cancer patients, even in the adjuvant scenario. Thus, obesity is a potential risk factor for breast cancer in postmenopausal women; therefore, prevention of weight gain and onset of obesity should be avoided to postpone or prevent some kinds of breast cancer.

Conflicts of Interests

The authors have no conflicts that are directly relevant to the content of this study.

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Authors contribution

Swati Sucharita Mohanty wrote the review after consideration of the entire literature, with Prafulla Kumar Mohanty. Both authors have thoroughly gone through the manuscript and have approved it.

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