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## Chapter 4

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# Recovery of Estrogen Level in Obese Women Is Preventive against Cancer

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## Abstract

Obesity associated hormonal disorders mediate increased breast cancer risk during the whole life of women without any ambiguous interaction between obesity and menopausal status. Erroneous results regarding the breast cancer protective impact of obesity in young women derive mainly from the deceptively lower tumor incidence among them as compared with obese postmenopausal cases. Obesity is typically associated with dysmetabolism and endangers the healthy equilibrium of sexual hormone production and ovulatory cycles in women, which are the prerequisites not only for reproductive capacity but also for somatic health. Literary data support that anovulatory infertility and nulliparity are strong risk factors for breast cancer in young women either with or without obesity. Circulating estrogen level may be the pivotal regulator in mediating differences in adipose tissue distribution between pre- and postmenopausal women. In obese premenopausal women, female-like, gluteofemoral, subcutaneous fat deposition is typical and there is a low incidence of obesity associated dysmetabolism and sexual hormone imbalance in these cases. Consequently, it is not obesity but rather the still sufficient estrogen level, which may be protective against breast cancer risk in young females. By contrast, in obese postmenopausal cases, circulating estrogen levels are dramatically decreased and the adipose tissue distribution becomes more male-like, viscerally deposited, presenting a strong risk factor for dysmetabolism and breast cancer. In obese postmenopausal women, hormone replacement therapy (HRT) decreases the risk of breast cancer as the protective effect of estrogen substitution may counteract obesity related systemic alterations. Recognition of inverse correlation between circulating estrogen levels and breast cancer risk in obese women should advance our understanding of breast cancer etiology and promotes primary prevention measures.

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## Introduction

In young women, before menopause adiposity is erroneously regarded to exhibit a protective effect against breast cancer risk [1-5]. By contrast, in postmenopausal cases, particularly in the elderly, obesity confers a strong risk for breast cancer [2, 6]. Certain results justify an inverse relationship between the BMI and serum estradiol levels, particularly in the follicular phase of the cycle [7]. Clinical studies mistakenly suggest that obesity is advantageous against breast cancer, by means of defective estrogen synthesis in young women [1]. Conversely, postmenopausal obesity is regarded as strong risk factor for breast tumors, mediated by the erroneously presumed excessive estrogen production of adipose tissue mass [8-10]. Explanations for these supposed ambiguous correlations are in concordance with the preconception that high estrogen levels play crucial role in mammary carcinogenesis, while estrogen deficiency is protective [11].

Confusing and disturbing associations were published concerning obesity and breast cancer risk in postmenopausal women. Obese postmenopausal women, who had never used hormone replacement therapy (HRT) exhibited fairly high breast cancer risk [12]. By contrast, HRT use attenuates or abolishes the increased breast cancer incidence [13-15] suggesting a protective impact of female sexual hormones in aged obese women.

In young women, the results of clinical studies justify that obesity induces mild or moderate decrease in circulating estrogen levels reflected by their inclination to anovulatory infertility and long or irregular menstrual cycles [16]. At the same time, fertility disorders and nulliparity seem to be strong cancer risk factors for the female organs in either obese or lean young women [17].

Evidences, provided by clinical endocrinological studies regarding correlations between defective hormonal status of obese women and decreased breast cancer incidence, are inconsistent or fairly contradictory [1]. Considering the apparently ambiguous biological behavior as regards breast cancers arising in premenopausal and postmenopausal women, the existence of two distinct types of breast malignancies was presumed occurring before and after menopause [18, 19].

Obesity is a well-known cancer risk factor associated with different grades of insulin resistance and a disturbance of male to female circulating sexual steroid levels [20-22]. Obesity provokes alterations in the whole endocrine system conferred by an excessive circulatory androgen production at the expense of defective estrogen synthesis [23]. Nevertheless, the health benefit of pathologic states; such as overweight and obesity can hardly be justified at any age of women.

Breast cancer risk and obesity-associated hormonal alterations exhibit close correlation during the whole life of women. This study tries to reveal the sources of the misleading clinical and epidemiologic results suggesting the breast cancer protective effect of obesity in the young.

## Pathogenetic Mechanisms As Links between Obesity and Breast Cancer Risk

Obesity, particularly visceral fatty tissue deposition leads to insulin resistance, associated with diverse immunologic, metabolic and hormonal alterations mediating breast cancer risk (Figure 1). The main stream of obesity related alterations is a self-generating, progressive insulin resistance in thorough interplay with the dysmetabolism and inflammation of adipose tissue mass and with an imbalance of sexual steroid production in the endocrine organs.

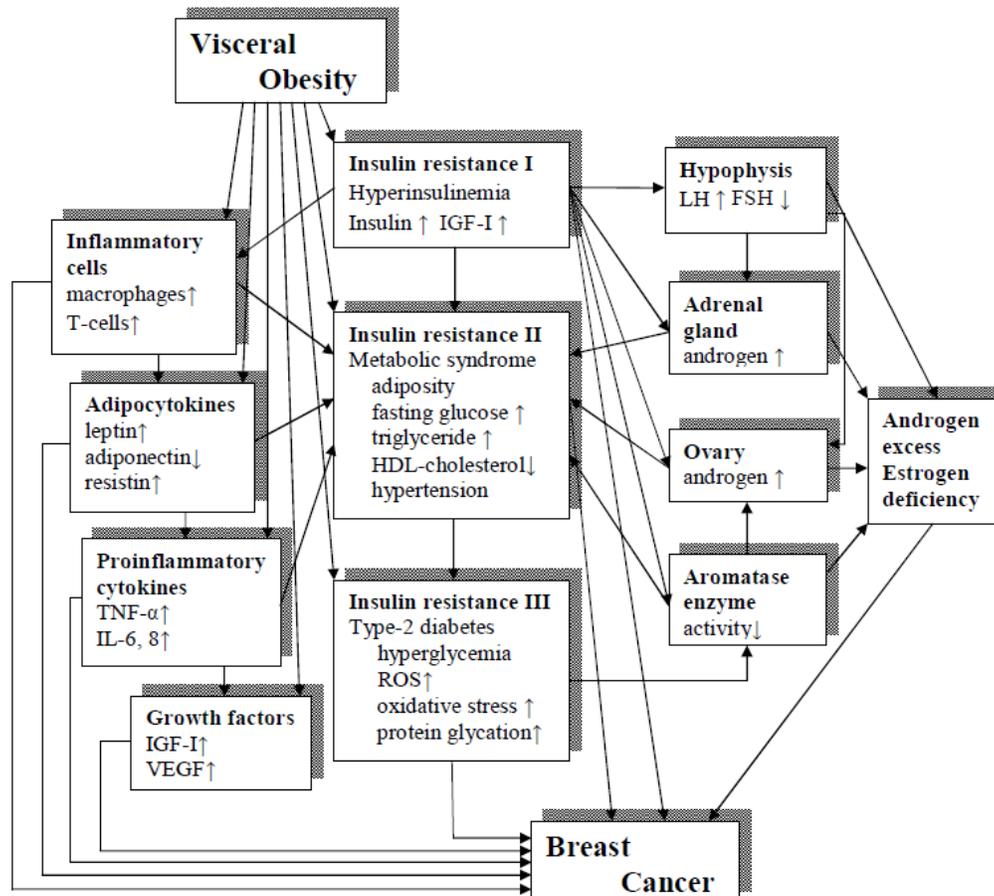


Figure 1. Pathogenetic mechanisms of obesity-related risk for breast cancer.

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### Obesity Related Insulin Resistance

Insulin resistance (IR) is a defect of insulin-mediated cellular glucose uptake, which may elicit many disorders in the gene regulation of cellular metabolism, growth, differentiation

and mitotic activity. IR predisposes patients to a variety of diseases, such as metabolic syndrome, type-2 diabetes, cardiovascular lesions and malignancies at different sites [24].

*Reactive hyperinsulinemia* in the first, compensated phase of insulin resistance maintains serum glucose level within the normal range by means of an increased secretory capacity of insular  $\beta$ -cells [25]. Insulin functions as a growth factor as well with strong mitogenic capacity [26]. High insulin level in itself may be regarded as cancer risk by the excessive synthesis and mitogenic activity of other, insulin-like growth factors, such as IGF-I. High levels of insulin and IGF-I have important role in the alterations of cell proliferation and in tumor induction, particularly in breast and prostate [27]. Insulin and IGF-I levels exhibit positive associations with breast cancer risk suggesting that hyperinsulinemia may be a substantial link between obesity and mammary carcinogenesis [28].

*Metabolic syndrome (prediabetes)* develops in the second, partially uncompensated phase of insulin resistance when the enhanced insulin synthesis is not enough to maintain euglycemia. This is a quartet of elevated fasting glucose, high serum triglyceride, low HDL cholesterol level and hypertension, being characteristic of viscerally obese patients [29]. Each of these symptoms alone is risk factor for cancer, and together they mean a multiple risk [30, 31].

*Hyperglycemia* provokes deliberation of free radicals causing derangements in both DNA and enzymes participating in repair mechanisms [32, 33]. High serum glucose level leads to a non-enzymatic glycation of protein structures, and the glycated products enhance the deliberation of free radicals, cytokines and growth factors [34]. Results of a prospective study justified that hyperglycemia among insulin resistant women exhibits direct correlation with mammary cancer risk [35].

*Dyslipidemia* is a complex disturbance of the lipid metabolism associated with insulin resistance and hyperinsulinemia [36]. Serum level of triglycerides shows close parallelism with insulin resistance, serum insulin level and BMI, whereas being inversely correlated with the high density lipoprotein (HDL) level. Results of clinical examinations justified the close association between hypertriglyceridemia and malignant tumors, particularly in breast cancer and colorectal cancer cases [37, 38, 39].

*Hypertension* usually shows close positive correlation with obesity, insulin resistance and hyperinsulinemia [40, 41]. Elevated insulin level is closely associated with increased activity of the sympathetic nervous system resulting in adrenergic vasoconstriction and hypertension [25, 42]. Activation of the renin-angiotensin-aldosterone system and subsequent elevations in angiotensin II and aldosterone levels are frequently seen in metabolic syndrome [43]. In postmenopausal hypertension, increased androgen/estrogen ratios play an important causal role. In older women, hypertension proved to be a strong risk factor for hormone dependent tumors, separately from obesity [44]. Time-dependent covariate analyses indicated a positive association between the metabolic syndrome and breast cancer, due primarily to positive associations with serum glucose, serum triglycerides, and diastolic blood pressure [45, 46, 47].

*Type-2 diabetes* is the uncompensated phase of insulin resistance when the decreased serum insulin level results in hyperglycemia. The disrupted glucose homeostasis, the excessive formation of free radicals and the protein glycation depress the activities of the antioxidant scavengers and enzymes [32, 48]. The role of free radicals and oxidative stress in the process of carcinogenesis is a well-known fact [49, 50]. Type-2 diabetes seems to be an independent risk for cancer development [51], particularly for breast cancer [39, 52, 53].

## Alterations in the Sexual Steroid Production in Obese Patients

Excessive insulin synthesis in obese women may contribute to *hyperandrogenism* and anovulatory infertility through several pathways as insulin is a potent regulator of sexual steroid production in the endocrine organs [54]. Hyperinsulinemia and excessive IGF-I supply stimulates *ovarian androgen production* at the expense of reduced estrogen synthesis [55]. High insulin level was found to increase the testosterone biosynthesis of human ovarian thecal cells deriving from insulin resistant, infertile women with polycystic ovarian syndrome (PCOS) [56]. Therapeutic improvement of insulin sensitivity and effective reduction of insulin secretion normalized serum free testosterone level [57, 58].

High insulin level may favor the *luteinizing hormone (LH) secretion of pituitary*, which also stimulates the androgen biosynthesis of adrenal gland and ovarian theca cells [59, 60]. Breast cancer risk is increased not only in hyperandrogenic postmenopausal women, but also in young cases with mild hyperandrogenism and apparently normal (ovulatory) menstrual cycles [61]. In centrally obese, either premenopausal or postmenopausal women, excessive ovarian testosterone production seems to be a genetically determined risk for breast cancer [62, 63].

Hyperinsulinemia and excessive IGF-I activity mediate *defective estrogen synthesis* by counteraction to aromatase enzyme gene expression. The aromatase enzyme complex catalyzes the conversion of androgens to estrogens in a wide variety of tissues. In premenopausal women, the ovaries are the principle sources of estradiol; by contrast, in postmenopausal women when, it is synthesized in a number of extragonadal sites [64]. These sites include the adipose tissue, breast, endometrium, bone, endothelium, aortic smooth muscle cells, and numerous locations in the brain. All these tissues, particularly breast and endometrium, have high estrogen demand and a local hormone synthesis helps to preserve their structural integrity and functional activity in spite of low circulatory estrogen levels [65].

In premenopausal women with type-2 diabetes, the ovaries exhibit decreased capacity to convert androgen to estrogen, probably due to a reduction of ovarian aromatase activity [66]. In patients with either estrogen deficiency (aromatase deficiency) or estrogen resistance (estrogen receptor mutation) glucose intolerance, hyperinsulinemia and lipid abnormalities are concomitant alterations associated with excessive androgen levels [67].

Estrogens decrease low grade inflammatory reactions and may in parallel reduce the glucocorticoid responses. Low estrogen levels after menopause allow the predominance of glucocorticoids. These observations suggest that the disturbed equilibrium between sex hormones and glucocorticoids may be a critical element in the manifestation of metabolic syndrome-related pathologies [68].

## Inflammatory and Metabolic Dysfunctions of Adipose Tissue in Visceral Obesity

Visceral adipose tissue has important functions by means of secretion of signaling molecules; adipokines, which regulate the cellular microenvironment both locally and systemically [69-71].

The chronic low grade inflammation associated with obesity is an important player in tumor development and progression. Increased IGF-I level may mediate the inflammation via

its effects on immunologically active cells including macrophages and T cells. [72]. IGF-I may provoke macrophage migration and invasion and increased production of proinflammatory cytokines.

Adipokines include unique products of fatty tissue known as *adipocytokines*; such as leptin, adiponectin resistin, etc. [73]. Leptin biosynthesis is in close direct correlation with insulin level and this may explain the increased leptin levels observed in obesity [74]. High leptin concentrations may constitute a possible link relating obesity and breast cancer promoting the invasion and migration of tumor cells [75]. Conversely, obesity may downregulate the secretion of adiponectin, an adipokine with anti-inflammatory, insulin sensitizing and anti-tumor properties [76]. The balance of leptin and adiponectin concentrations are the critical factors in breast cancer risk and in other obesity related cancer genesis [77].

Cytokines (TNF- $\alpha$ , IL-6, IL-8) produced in excessive adipose tissue mass increase nitric oxide (NO) and reactive oxygen species (ROS) concentration. Accumulation of cytokines and ROS further contribute to insulin resistance. All signaling molecules of fatty tissue including cytokines, hormones and growth factors are involved in the proliferation, invasion and metastatic spread of tumors including breast cancer [78, 79].

## **Protective Effects of Estrogen against Obesity and Obesity Associated Alterations**

Estrogens promote, maintain and control the ideal distribution of body fat [80]. These steroids are known to regulate differentiation and metabolism of adipocytes as well. Estrogen deficiency and defective estrogen signaling results in obesity, preferentially in visceral location [20, 80].

### **Anti-Obesity Effects of Estrogen**

Estrogen regulates the metabolism, differentiation, growth and cell kinetic mechanisms of adipocytes. In healthy premenopausal women central adipocytes show higher insulin sensitivity and a higher turnover rate than male cases with similar fat content [81]. After menopause, decreased ovarian estrogen synthesis results in increasing insulin resistance in central adipocytes and higher fasting insulin levels conferring increased risk for metabolic and cardiovascular diseases [82, 83]. Estradiol is able to inhibit the glucocorticoid production in rodent adipocytes of mesenteric origin, providing novel insight into the anti-obesity mechanism of estrogen effect [84].

Obesity is important concomitant of insulin resistance and it is strongly associated with disturbed equilibrium of male to female sexual hormone concentrations in women [85]. Healthy estrogen predominance in women induces subcutaneous gluteofemoral adipose tissue deposition [82]. Conversely, androgen excess and deficient estrogen synthesis exhibits close correlation with visceral obesity both in pre- and postmenopausal women [23]. In young women with PCOS, treatment with oral contraceptives protects from the development of endometrial carcinoma, regularizes menses and ameliorates hirsutism, acne and obesity [86].

Similarly, in obese postmenopausal women with or without type-2 diabetes, HRT reduces abdominal adiposity and insulin resistance [87] and decreases the risk for obesity associated breast cancer [15].

### Anti-Atherogenic and Anti-Hypertensive Effects of Estrogen

Healthy premenopausal women are typically protected from cardiovascular diseases and hypertension as compared with men. Conversely, obese, diabetic young women, and postmenopausal cases may lose this protected state as their bioavailable estradiol levels are strongly reduced [88].

Estrogen may have crucial role in the maintenance of normal serum lipid levels. Postmenopausal women exhibit a shift toward a more atherogenic lipid profile in estrogen deficient milieu [89]. Postmenopausal estrogen therapy may reduce the risk of cardiovascular disease, which effect may be attributed to favorable changes in plasma lipid levels [90]. Estrogens have important regulatory role in the hepatic lipid metabolism as well. In aged rats, estradiol administration lowered the level of lipid peroxidation and improved the dysfunction parameters of the liver [91].

Estradiol has cardiovascular protective impact by its anti-hypertensive activity as well. It downregulates the components of the renin-angiotensin system (RAS) and reduces the expression and activity of angiotensin I-converting enzyme [92, 93]. Estradiol inhibits the excessive synthesis of vasoconstrictor endothelin and improves endothelial dysfunction in ovariectomized female spontaneously hypertensive rats [94]. In the pathogenesis of postmenopausal hypertension increased androgen to estrogen ratio may be associated with the activation of renin-angiotensin and endothelin systems [95].

Estrogens are protective against the stiffness of vessel walls. The relationship between collagen content and distensibility of the human uterine artery and estrogen receptor  $\alpha$  expression was studied on biopsy samples obtained from women undergoing hysterectomy [96]. A functional correlation was observed between the high estrogen receptor  $\alpha$  content and lower collagen concentration, indicating that estrogen through activation of estrogen receptor  $\alpha$  protects against vascular collagen accumulation making the vessel more distensible.

The rate of hypertension fairly increases after menopause. In general it seems that, despite some negative data on subgroups of elderly postmenopausal women obtained with oral estrogens, HRT exhibits anti-hypertensive impact [97]. Majority of the results indicate neutral or even beneficial effects of estrogen or estrogen-progestin administration on blood pressure control of both normotensive and hypertensive postmenopausal women.

Clinical and experimental studies support that estradiol has also antioxidant activities [98, 99] that may be effective against inflammatory lesions, atherosclerotic vessel injuries and malignancies.

### Antidiabetogenic Impacts of Estrogen

Estrogens have beneficial effects on the energy metabolism and glucose homeostasis [100]. Estrogens advantageously regulate the insulin production capacity of the *pancreatic islet cells* [83]. Estrogen receptor alpha (ER- $\alpha$ ) activation promotes  $\beta$ -cell mass survival and

insulin biosynthesis, whereas ER $\beta$  activation improves glucose stimulated insulin secretion [101]. Estrogen administration seem to be a therapeutic avenue to preserve functional  $\beta$ -cell mass in patients with diabetes mellitus.

*In the liver*, estrogen regulates insulin sensitivity by the balanced activation of glycogen synthase and glycolytic enzymes to maintain the equilibrium of glycogen synthesis and glycogenolysis. In ER- $\alpha$  knockout mice, hepatic insulin resistance was associated with decreased glucose uptake in skeletal muscles [102].

*In the peripheral tissues* ERs advantageously modulate the insulin stimulated glucose uptake through regulation of the phosphorylation of insulin receptor protein. In hyperinsulinemia, high concentrations of estradiol can inhibit the excessive insulin signaling in adipocytes [103] counteracting pathologic glucose uptake and dangerous mitogenic activity. ERs have crucial roles in glucose uptake by regulation of intracellular glucose transporters (GLUTs) and enhancing both GLUT4 expression and translocation [104]. In women with PCOS, decrease in insulin stimulated glucose uptake was associated with reduced amount of GLUT4 on adipocyte membrane [105].

ER signals have pivotal role in the regulation of growth hormone (GH) activity by means of modulation of its secretion and cellular GH receptor functions. Estrogens play a positive role in the regulation of GH-IGF-I axis in both genders [106], which may be in close correlation with their antidiabetogenic and anticancer capacities.

Postmenopausal hormone replacement therapy (HRT) reduced abdominal obesity, insulin resistance, new-onset diabetes, hyperlipidemia, blood pressure, adhesion molecules and procoagulant factors in women without diabetes and reduced insulin resistance and fasting glucose in women with diabetes [87].

### Regulation of Adipokine Secretion, Inflammatory Reactions and Growth Factor Activity by Estrogen

At early stages of estrogen deficiency, estrogen administration decreased the inflammation associated risk of developing cardiovascular disease [107]. Estradiol may contribute even to the vascular healing process and to the prevention of lumen restenosis in atherogenic arteries. It improves reendothelialization through ER- $\alpha$  activation and decreases smooth muscle cell migration and proliferation through ER- $\beta$  stimulation [108].

Phytoestrogens may advantageously influence the level of adipokines in insulin resistant women. In postmenopausal cases, diet, physical exercise and daily oral intake of soy isoflavones had a beneficial lowering effect on serum leptin, and TNF- $\alpha$  levels and showed a significant increase in mean serum levels of adiponectin [109]. Epidemiologic studies support that phytoestrogen rich foods may be beneficial consumed before or during adolescence for the prevention of breast cancer [110].

In clinical studies estradiol lowered, whereas testosterone increased total IGF-I level and estradiol specifically suppressed unbound, free IGF-I level [111]. Crosstalk between estrogen receptors and growth factor (IGF-I, EGF, VEGF) receptor signaling pathways is well-known both in healthy tissues and malignancies [112, 113]. Nevertheless, estradiol may induce both growth stimulation and growth inhibition depending on the ratio and activity of ERs and GFRs [114].

The presumed synergistic contribution of ERs and GFRs to cancer development and progression would be a permanent danger without contraregulatory impact. Inhibition of growth factor signaling in apparently ER-negative breast cancer cells successfully restored ER expression suggesting a dynamic, inverse relationship between the two receptor systems [115]. Moreover, excessive EGF predominance decreased both ER- $\alpha$  protein concentration and gene transcription activity in the human breast cancer cell line MCF-7 [116]. These results suggest an alternative role of estrogen and growth factor actions in tumor cell proliferation.

## **Correlations between Grade and Distribution of Obesity and Insulin Resistance**

Circulating estrogen level may be the key regulator in mediating differences in adipose tissue distribution between pre- and postmenopausal women [117]. In *obese premenopausal women*, peripheral, subcutaneous adiposity is typical and there is a lower incidence of obesity associated dysmetabolism. By contrast, in *obese postmenopausal cases*, estrogen levels are dramatically decreased and adipose tissue distribution becomes more male-like. Visceral adiposity and the associated metabolic and hormonal disorders mean high risk for obesity related diseases, included breast cancer [69]. Body mass index (BMI) and weight in kilogram [4, 5, 118] reflects general adiposity. BMI or body weight in kilogram may not correctly reflect the correlations among obesity, hormonal disturbances and breast cancer risk in young women [14]. Body circumference measurements; such as hip (HC), waist (WC) and waist to hip ratio (WHR) inform about the regional distribution of fatty tissue deposition [119-121] and the mass of visceral abdominal fat, reflecting the metabolic risk of patients. WC, HC and WHC ratio have important role in the prediction of premenopausal breast cancer occurrence [119, 122]. Conversely, in other studies, body fat distribution, such as WC had no defining role in the establishment of insulin resistance or premenopausal breast cancer risk [2, 119]. Magnetic resonance imaging (MRI) quantified separately the mass of visceral and subcutaneous abdominal fat depositions in obese adolescent girls [123]. Mass of visceral fat was highly correlated with insulin secretion and insulin resistance. Conversely, abdominal subcutaneous fat mass did not show close correlation with the quantified indicators of insulin resistance. In conclusion, neither BMI nor circumference measurement may exactly separate the metabolically indifferent, subcutaneous fat and the visceral fat endangering insulin sensitivity. These correlations may partially explain the controversial links between obesity grade and breast cancer risk.

## **Lifelong Changes in the Estrogen Level of Women and Their Relation to Obesity and Breast Cancer Risk**

Female sexual steroid levels and fertility continuously decrease during the life of women. The ability to conceive is at its peak in young women under 30 years of age with a continuous

decline of fertility from the fourth decade [124]. Menopause at 50-51 years of age means a sudden break in ovarian estrogen synthesis and confers further decline in the hormone levels.

In premenopausal women, the good equilibrium of sex steroid synthesis defines health and reproductive capacity, whereas good, symptom-free adaptation to the estrogen deficient environment is a prerequisite of postmenopausal health. Changes in the hormonal equilibrium during women's lives strongly influence the obesity associated breast cancer risk (Table 1).

**Table 1. Lifelong changes in the hormonal status of obese women and their breast cancer risk**

Life periods of obese women	Estrogen level	Insulin resistance	Breast cancer risk
<b>Children</b>	↓	↑	↑
<b>Adolescent girls</b>	↓↓	↑↑	↑↑
<b>Premenopausal women</b>			
type-2 diabetes	↓	↑	↑
anovulation	↓	↑	↑
nulliparity	↓	↑	↑
contraceptive use	↑	↓	↓
multiparity	↑	↓	↓
in vitro fertilization	↑	↓	↓
<b>Postmenopausal women</b>			
HRT user	↑	↓	↓
non HRT user	↓	↑	↑
type-2 diabetes	↓↓	↑↑	↑↑
hysterectomy	↓↓	↑↑	↑↑

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### Obesity Associated Hormonal Alterations in Childhood and Adolescence and Their Prediction for Breast Cancer Risk

Obesity is a detrimental disorder and may not be protective against malignancies even in children. *Childhood obesity* is associated with insulin resistance and hyperinsulinemia mediating risks for chronic diseases and cancer in the adult life [125]. Many factors of metabolic syndrome, even type-2 diabetes might occur in these young prepubertal obese cases [126].

Some studies suppose a definite key age; for example 10 years when breast cancer “protective” obesity turns to harmful as a prediction of elevated breast cancer risk in the premenopausal life [127]. Others found fatness in childhood to be associated with decreased breast cancer risk for both pre- and postmenopausal women [128]. Further authors postulate that only teenager obesity is protective against premenopausal breast cancer but after teenage years it may confer an increased risk for postmenopausal breast cancer [129]. Nevertheless,

finding a key age at which obesity in young girls turns from a cancer protective to a cancer promoting agent seemed to be unsuccessful.

*Obesity in puberty* with extreme somatic growth and explosion-like sexual development means a great challenge for the entire metabolic and hormonal systems. In obese children, puberty becomes a more serious danger for insulin resistant states as compared with normal weight cases [130, 131]. In obese adolescent patients, increased insulin resistance does not return to prepubertal values and represents high risk for adult metabolic syndrome, type-2 diabetes and for their complications [126, 132].

In adolescent girls, obesity associated metabolic storms are related to abnormal ovarian sexual steroidogenesis as well, resulting in excessive androgen and defective estrogen production and greater frequency of irregular, anovulatory cycles [129, 133, 134]. High serum androgen concentrations developing in puberty are preserved into adulthood and are reflected by defective fertility at least until 30 years of age [133, 134]. This observation may be in concordance with an increased premenopausal breast cancer risk of delayed first childbearing [19, 135].

Equilibrium of sexual hormone production and the development of regular cycles are prerequisites not only for reproduction but also for somatic health in women [20, 21, 136]. Pathological alterations in the critical period of puberty, such as obesity endangering both the fertility and survival of women might not be protective against cancer initiation in either pre- or postmenopausal cases.

### Associations between Obesity Related Anovulatory Menstrual Cycles and Breast Cancer Risk in Premenopausal Women

In premenopausal cases, obesity is associated with defective estrogen synthesis and decreased circulatory estrogen levels, particularly in the follicular phase [7]. These obesity-related hormonal alterations may usually confer irregular menstrual cycles, anovulation, infertility and reduced response to fertility treatment [16]. Theory of estrogen induced mammary carcinogenesis supports the hypothesis that in obese young women, anovulation and the associated menstrual cycle disorders may be protective against breast cancer risk [137].

Results of cohort and case-control studies exhibit inconsistent data concerning the associations of menstrual disorders and breast cancer incidence. Some investigators found an increased breast cancer incidence in women with long menstrual cycles [138, 139] others found no associations [140-142] or conversely, a decreased risk [137, 143, 144]. In a large study, the results were quite controversial, in women having long cycles the risk of breast cancer was increased, whereas, in those whose cycle was estimated to be irregular, the risk was reduced [145]! In a prospective study, anovulatory infertility was associated with decreased breast cancer incidence [146], while a further study established that other factors than anovulatory disorders may be protective against breast cancer risk in obese young women [116].

Anovulation and menstrual irregularities are strong risk factors for breast cancer both in obese cases and non-obese controls. Among symptom-free lean control girls, hyperinsulinemia and excessive androgen concentration may reveal the insulin resistance and occult anovulatory cycles [24].

In premenopausal women with polycystic ovarian syndrome (PCOS) the coexistence of anovulatory infertility and insulin resistance represents common risk for the cancers of highly hormone dependent breast, endometrium and ovary [147, 148]. In the UK, breast cancer was the most common cause of death among women with PCOS [149]. In a Brazilian study, anovulatory disorders with or without PCOS were promoters of endometrial and breast cancer among infertile women [150]. In an American study, nulliparity, irregular menstrual cycles, obesity, diabetes and hypertension were strongly associated with endometrial cancer risk in premenopausal women [151]. In young, nulliparous women, endometrial carcinomas were frequently associated with synchronous primary cancers of the ovary or breast [151, 152].

In premenopausal women, high prolactin level is also associated with cycle disorders, reproductive dysfunction and hyperandrogenism as well as increased overall cancer risk [153]. Data of recent studies suggest positive association between elevated prolactin level and breast cancer risk, predominantly among young, premenopausal cases [154].

In young women, slight or moderate decrease in circulating female sexual steroid levels may be enough to block the delicate mechanism of ovulation. At the same time, a slightly estrogen deficient milieu confers preferential cancer risk for the female organ triad having high estrogen demand [20, 136].

### Correlations between Reproductive Data and Obesity-Associated Breast Cancer Risk in Premenopausal Women

In women, multiparity and risk for malignancies at several sites exhibit an inverse relationship [155-157]. High parity shows tumor protective effect even against female breast, endometrial and ovarian cancers [158, 159]. This may be attributed to the good equilibrium of female sexual steroid production associated with good fertility. Moreover, pregnancy equivalent, high female sexual hormone treatment could prevent the chemically induced mammary carcinogenesis in female Lewis rats [160].

By contrast, nulliparity may be associated with ovulatory disorders in the majority of cases and certain studies equivocally established an increased prevalence of breast cancer in nulliparous women [161, 162]. Furthermore, coexistence of nulliparity and overweight may amplify each other's effect on increasing breast cancer risk [161]. Delayed first childbearing may also be associated with long term sex hormone imbalance and fertility disorders, and proved to be a risk factor of breast cancer [19, 135]. High breast cancer risk in correlation with nulliparity and delayed first birth suggests an important role of defective estrogen synthesis in anovulatory disorders and mammary carcinogenesis.

Role of fertility medications in the increased risk of breast cancer has been hypothesized but large studies were not able to find any associated risk of breast cancer after ovulation provocation and in vitro fertilization (IVF) [163]. Moreover, an American case-cohort study established that use of clomiphene as treatment for infertility lowers the increased risk of breast cancer in women with ovulatory abnormalities [164].

Overall cancer risk among infertile women before IVF was found to be markedly increased in a large study in Sweden [165]. After IVF assisted childbirth, cancer risk was significantly decreased mainly due to a lower than expected risk for breast and cancer. These recent literary data support the breast cancer lowering value of IVF assisted childbirth among endangered anovulatory women.

## Correlations between Postmenopausal Obesity and Breast Cancer Risk in Women

In postmenopausal estrogen deficient, obese cases the regional distribution of fat deposition near uniformly affects the visceral region in close correlation with their high breast cancer risk [6].

*Obese postmenopausal women never using HRT* are obviously insulin resistant. Ageing after menopause further increases the cancer risk as it is associated with a continuous estrogen loss and advancing insulin resistance [166]. In old obese women, struggle between the harmful insulin resistance and the low level of protective female sexual steroids will be frequently finished by cancer initiation. These correlations explain the higher breast cancer risk of obese postmenopausal women who do not receive hormone treatment as compared with HRT users.

In *obese HRT user postmenopausal women* the incidence of breast cancer is equivocally reduced [15]. The protective effect of estrogen substitution may counteract the obesity associated insulin resistance and their breast cancer risk decreases [17]. Estradiol substitution increases insulin sensitivity [100], yields favorable changes in plasma lipid levels [90] and by its anti-obesity effect decreases the accumulation of visceral fat deposition [167]. All these impacts justify the beneficial anticancer capacity of HRT in obese women after menopause.

A great challenge is to explain the beneficial anticancer impact of HRT in obese postmenopausal women based on the misbelief that they have excessive circulatory estrogen level. Some authors assumed that mediators other than estrogen, such as insulin and insulin-like growth factors might confer the obesity associated breast cancer risk after menopause [28].

## Insulin Resistance and Sexual Hormone Imbalance in Non-Obese Control Women

Insulin resistance is a fairly heterogeneous disorder for which both genetic and environmental factors jointly determine susceptibility [168]. The most important environmental component is reflected by the global shift toward a western lifestyle, including overeating and sedentary habits [169]. Moreover, night shift workers and dark skinned immigrants in northern countries are particularly endangered by the defect of glucose uptake. Poor natural light exposure induces excessive melatonin synthesis, which confers deleterious hormonal imbalance; such as insulin resistance, deficiencies of estrogen, thyroxin and vitamin D [170].

In women, insulin resistance and disturbed equilibrium of sexual steroids are not closely associated with high energy intake or obesity. In a case control study, women with PCOS and healthy, ovulatory controls were compared by means of anthropometric, laboratory and nutritional investigations [171]. Hyperandrogenism, dyslipidemic alterations as well as increased postprandial glucose and insulin levels were characteristic findings in PCOS cases, which were not associated with high energy intake or diet composition. Insulin resistance in non-obese subjects was associated with impaired insulin signaling in skeletal muscles [172], and with the oxidative damage in relation to the byproducts of oxidative stress [173].

The pathogenesis of insulin resistance in the absence of obesity may be in close correlation with defective estrogen signaling [174]. Since estrogen receptors are pivotal regulators of all phases of cellular glucose uptake, either deficient estrogen exposure or defective estrogen receptor signaling may result in metabolic disorders and their comorbidities [175].

A case report on a 28-year-old girl with XX chromosome presented the cardinal features of mutation in the single human gene encoding aromatase P450 (CYP19) [176]. In aromatase deficiency syndrome, the basal concentrations of plasma androgens were highly elevated, whereas plasma estradiol was extremely low. By the age of puberty, she developed progressive signs of virilization with no signs of estrogen action; hypergonadotropic hypogonadism, polycystic ovaries, and tall stature. Hormone replacement therapy led to breast development, regular menstrual cycles, resolution of ovarian cysts, and suppression of the elevated FSH and LH values. Findings in this rare case of aromatase deficiency suggest that the development of polycystic ovaries is primarily associated with low estrogen exposure, and insulin resistance may be the secondary alteration.

In women, insulin resistance is closely associated with hyperandrogenism as well. In women with hirsutism, insulin resistance proved to be a characteristic finding regardless of their body mass index [177].

In conclusion, insulin resistance and anovulatory infertility, which are strong risk factors for mammary tumors, may occur in both obese cases and non-obese control women [17]. Erroneous results suggesting the breast cancer protective effect of obesity in premenopausal women may derive from the high rate of healthy cases among young women with predominantly female-like obesity. At the same time, disregarding the possibility of insulin resistance and increased male-to-female sexual steroid level ratio in lean control women yields further misleading results, as these alterations are stronger risk factors for breast cancer than obesity alone.

## **Exogenous Hormone Use for Prevention and Treatment of Breast Cancer**

*Oral contraceptive (OC) use* replaces the natural menstrual cycle with relatively steady levels and fluctuations of artificial sex hormones. In PCOS cases, treated with OCs, the volume of cystic ovaries is reduced, ovarian testosterone secretion is decreased and there are favorable effects on carbohydrate and lipid metabolism as well [178].

Combined oral contraceptives provide substantial protection against endometrial and ovarian cancer in the endangered anovulatory women [178, 179]. Effect of OCs on breast cancer risk seems to be controversial. Increased risk was confined to women who have begun pill use as teenagers or those with very long term use [179]. Nevertheless, endometrial, ovarian and breast cancers exhibit conspicuously similar epidemiology and they frequently synchronously appear in anovulatory young women [151, 152]. These observations may suggest that a proper selection of patients and controls would lead to the realistic evaluation of beneficial OC effect even on breast cancer risk.

*Use of HRT* has highly controversial associations with breast cancer risk. Till now, the carcinogenic capacity of postmenopausal estrogen therapy was a prevailing concept [180].

By contrast, recent literary data support the cancer protective capacity of postmenopausal estrogen treatment both for the moderately and highly hormone responsive organs of women [135, 181].

In 2011 the WHI Randomized Controlled Trial strengthened that the estrogen treatment in women with prior hysterectomy resulted in a significantly lower risk for breast cancer than in untreated controls [182]. Breast cancer risk of women with hysterectomy may be near uniformly high because of their abrupt, shocking hormone deprivation. HRT studies on these homogenously selected cases seem to be methodologically fairly strong, yielding unexpectedly correct results [135, 181].

Increasing number of evidences from the clinical trials suggests that unopposed estrogen as hormone treatment does not increase the risk of breast cancer, and may even reduce it. The earlier beliefs regarding the breast cancer risk of hormone replacement therapy are completely changing [182-187]. The new concepts concerning breast cancer etiology provide completely new strategies against mammary tumors (Table 2 and 3).

**Table 2. Hormonal risk factors for breast cancer**

<b>Traditional concept</b>	<b>Author's new concept</b>
Excessive circulatory estrogen level	Reduced circulatory estrogen level
Increased aromatase activity	Defective aromatase activity
Unopposed estrogen level	-----
Ovulatory peak of estrogen level	Anovulatory disorder
Contraceptive use	Defective hormonal cycle
Xenoestrogens	-----
Hormone replacement therapy	Missing hormone replacement therapy
Excessive light exposure	Light deficiency
Androgen excess	Androgen excess
Hyperinsulinemia	Hyperinsulinemia

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**Table 3. Protective hormonal factors against breast cancer**

<b>Traditional concept</b>	<b>Author's new concept</b>
Obesity (in young)	Normal weight
Anovulation	Healthy ovulatory cycles
Hysterectomy (preventive)	Preservation of gynecological organs
Anti-estrogen (preventive)	Estrogen prevention

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Before the introduction of antiestrogens, high dose estrogen was successfully administered as endocrine therapy for postmenopausal women with advanced breast cancer. Nowadays, the ambiguous, unreliable therapeutic effects and high toxicity of antiestrogens suggest the necessity of finding new strategies for breast cancer treatment [188]. Recently, the

old-fashioned high-dose estrogen treatment in patients with advanced breast cancer and previous estrogen deprivation was demonstrated to be effective in prospective clinical trials. Anti-tumor mechanism of estrogen therapy is under debate, but one can hypothesize that after a long-term antiestrogen treatment estrogen may become an apoptotic trigger rather than a survival signal for breast cancer cells [189]. Today, we are on the route to regard estrogens as beneficial anti-cancer drugs rather than carcinogenic agents.

## Conclusion

Obesity-associated hormonal disorders confer breast cancer risk during the whole life of women without any ambiguous interaction between obesity and menopausal status. Erroneous results regarding the breast cancer protective effect of obesity in young women derive mainly from the deceptively lower tumor incidence among them. Further misleading factor may be that hormonal disorders related to anovulatory infertility are strong cancer risk factors for the breast in both obese and non-obese young women.

*Low incidence rate of breast cancer* in young obese women may be a very important misleading finding. In the majority of premenopausal obese cases a predominantly subcutaneous adipose tissue deposition results in milder insulin resistance being counteracted by their preserved hormonal cycle. Consequently, in obese premenopausal women their circulatory estrogen level confers protective effect against breast cancer rather than obesity.

A long term exposition to harmful environmental and systemic factors is necessary for cancer initiation; moreover the tumor growth from the initiation to clinically diagnosable size takes further several years. This double delay of clinical appearance of breast cancers may frequently result in a postmenopausal tumor, though it was initiated in the premenopausal period.

*Anovulatory infertility and the associated hormonal defects* seem to be stronger breast cancer risk factors than adiposity alone and these alterations are not rare even among control cases with normal weight. Studies on obesity-related breast cancer risk disregarded the random occurrence of these hormonal alterations both among obese cases and lean controls. Moreover, oral contraceptive use is fairly widespread among premenopausal women, which may reverse the mild hormonal defects and attenuates their cancer risk either in obese or in lean cases. Strict selection of healthy, lean control women for obesity associated breast cancer studies and taking into account the OC use among obese cases and controls will justify the health advantage of normal body weight over obesity.

Recognition of the inverse correlation between circulatory estrogen-level and breast cancer risk in obese women should advance our understanding of breast cancer etiology. Moreover, it would promote primary cancer prevention measures and the introduction of causal cancer therapy.

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