

Body Adiposity, Body Fat Distribution, Sex Hormones and Risk of Breast Cancer

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Obesity has been well documented to increase the risk of several diseases such as cardiovascular disease, diabetes, hypertension and gall bladder disease⁽¹⁻³⁾. Obesity is defined as a state of adiposity in which body fatness is above the ideal. A body mass index (BMI) of 27 or greater generally indicates obesity and increasing risk of developing health problems⁽⁴⁾. The most frequently used measure of body fat distribution is the waist to hip ratio (WHR). The WHR is also called the abdominal/gluteal ratio which differentiates between android, characterized by the "apple shape" typical of men, and gynoid, characterized by the "pear shape" common to women, obesity. The waist or abdominal circumference is defined as the smallest circumference between the rib cage and the umbilicus, and the hip circumference as the largest circumference between the waist and the knees⁽⁵⁾. Abdominal or android obesity is indicated by a WHR of 1.0 or greater in men and 0.8 or greater in women⁽⁶⁾. Other measures such as the subcutaneous fat distribution, i.e., skinfold measures at various body sites such as the chest, subscapular, suprailiac, biceps, triceps, abdominal, and thigh areas have also been used to measure regional fat distribution.

Growing evidence suggests that obesity may be a risk factor for the development of endometrial, and ovarian cancers^(7,8). Several studies have also demonstrated an association between degree of adiposity and breast cancer⁽⁹⁻¹²⁾. Obese women are more likely to have menstrual disturbances, and have been shown to have elevated levels of non-protein bound and total estrogens⁽¹³⁻¹⁵⁾. Compared to controls, women with breast cancer have higher levels of non-protein bound estradiol and albumin-bound estradiol⁽¹⁶⁻²⁰⁾, lower levels of sex-hormone-binding globulin (SHBG)^(21,22), and a decrease in SHB capacity^(17,18,22). The sex steroids are bound to SHBG with high affinity and to albumin with much lower affinity^(23,24). It is the fraction of sex steroids that is not bound to SHBG and the very loosely albumin bound

sex steroids, and not the total concentration of sex steroids, that are available for biological activity on the breast^(16-19,25). In addition, the level of SHBG determines the amount of available estrogen that can interact with the breast⁽²⁶⁾.

Although several investigators found either decreased⁽²⁷⁾ or no difference^(21,28) in the levels of estrone and/or estradiol-17-beta in obese women compared to normal weight subjects, others have reported that in both pre- and postmenopausal women, the greater the level of obesity, the greater the proportion of bioavailable estradiol, i.e., the nonprotein bound and albumin bound components, and the lower the total levels of SHBG, and the SHBG capacity to bind^(15,26,29,30). The findings that increased weight was associated with an early age at menarche and with a late age at menopause, both well-recognized risk factors for breast cancer^(31,32), indirectly support the relationship between obesity and hormones and breast cancer. The increased biological availability and activity of estrogen due to general adiposity may be via alterations in estrogen protein binding⁽³³⁾, postmenopausal estrogen production⁽³⁴⁾, increased conversion of estrone and estradiol from their precursors by aromatase enzymes in the lipocytes⁽¹⁵⁾, and 2-versus 16-hydroxylation of estradiol⁽³⁵⁾.

Growing evidence also suggests that body fat distribution is an important risk factor in the development⁽³⁶⁾ and prognosis⁽²⁶⁾ of breast cancer. A higher incidence of breast cancer has been suggested to be directly related to abdominal adiposity^(8,36). A recent study suggests that "increased central to peripheral body fat distribution predicts breast cancer risk independently of the degree of adiposity and may be a more specific marker of a premalignant hormonal pattern than degree of adiposity"⁽⁸⁾. These findings are supported by another recent study which showed an increased risk of breast cancer among postmenopausal women with increased waist to hip ratio⁽³⁷⁾. Hence, women on the typical high-fat, low-fiber Western diet which is mainly reflected by

abdominal fat accumulation⁽³³⁾, are possibly at higher risk of developing breast cancer.

Decreased binding of estrogen to sex hormone binding globulin (SHBG) has been associated with both abdominal obesity and increased abdominal fat cell size⁽³³⁾. An increased localization of fat in the upper body in healthy premenopausal women was shown by Evans et al⁽³⁸⁾ to be associated with a continuous decline of plasma SHBG levels. Women with abdominal (i.e. central) obesity have been found by Kirschner et al⁽³⁹⁾ to have increased concentrations of free estradiol. While women with femoral (i.e. peripheral) obesity had higher amounts of estrone due to increased peripheral aromatization of androstenedione. Despite findings of increases in various forms of estrogen in women with femoral and abdominal obesity, the latter have been suggested by various studies^(33,40-42) to have greater increases in biologically significant estrogens.

As body adiposity and body fat distribution are risk factors that are potentially modifiable, studies determining the relationship between these factors and breast cancer risk are considerably important. Further studies are needed to determine whether or not, and if so, how changes in degree of adiposity and in body fat distribution over time affect the risk of breast cancer. Physical activity has been found to influence body composition and body fat distribution⁽⁴³⁻⁴⁸⁾, and to be associated with endogenous estrogen metabolism and levels of sex-hormone binding globulin (SHBG)^(43,49). More definitive studies are needed to establish the relationships of all three factors (body adiposity, body fat distribution, and physical activity) and levels of endogenous sex-hormones as well as the nature of their interactions. Long-term epidemiologic studies using large prospective cohorts of both pre and postmenopausal women whose diets, endogenous sex-hormones, body adiposity, body fat distribution, and level of physical activity are monitored with breast cancer as one of the outcome variables, for example, would add considerably to existing knowledge on these relationships and their interactions, as well as to knowledge on the etiology and progression of hormone-dependent breast cancer.

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