Minireview: Obesity and Breast Cancer: The Estrogen Connection

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There is now substantial evidence that overweight and/or obesity and/or weight gain are risk factors for the development of postmenopausal breast cancer. In addition, obesity and/or elevated body mass index at breast cancer diagnosis has a negative impact on prognosis for both premenopausal and postmenopausal women. Therefore, understanding the mechanism of how obesity affects the mammary tumorigenesis process is an important health issue. Elevated serum estrogen levels as well as enhanced local production of estrogen have been considered primary mediators of how increased body weight promotes breast cancer development in postmenopausal women. Here, we provide an overview of estrogen's relationship with both obesity and breast cancer as separate entities. Human and relevant preclinical studies are cited. In addition, other growth factors that may be involved in this relationship are considered. **(*Endocrinology* 150: 2537–2542, 2009)**

Epidemiological studies indicate that overweight and/or obesity, usually reflected by body mass index (BMI) [BWI = weight (kg) ÷ height (m^2)], is a risk factor for the development of postmenopausal breast cancer (1–14). Although obesity in premenopausal women has been associated with a decreased breast cancer risk, this may be unique to industrialized societies (15) and may be applicable only to younger obese women (16). More recently a prospective study conducted in Norway confirmed the protective effect of overweight and obesity for premenopausal breast cancer, but not for women with a family history of the disease (17).

Weight gain in adulthood also has been implicated as an important determinant of breast cancer risk (18–28). In fact a recent publication assessing breast cancer risk factors listed BMI and weight gain between the ages of 20 and 50 yr as second only to Gail Model parameters [quantitative breast density, free estradiol, parity (yes/no), and age of menopause] in importance (29). It has been suggested that body fat may be a better predictor of postmenopausal breast cancer risk than either body weight or BMI (30), and body fat distribution may also impact breast cancer risk (31–33). However, when conducting large-scale studies, measurements of body fat and body fat distribution are not as easily obtained as height and weight, which can then be used for calculating BMI.

Obesity also is associated with greater tumor burden in women diagnosed with breast cancer (34, 35) and with higher grade tumors (36–38). For both premenopausal and postmenopausal women, overweight/obesity is associated with poorer prognosis and/or increased mortality (14, 35, 36, 39–43). One recent study indicated that the BMI effect on mortality in postmenopausal women may be of greater impact in younger women (44).

With the incidence of overweight and obesity increasing throughout the world, the number of women at risk for developing breast cancer will also increase. For example, a quick calculation based on U.S. Census Bureau data indicates that there are about 45 million women in the United States between the ages of 45 and 75 yr, and it is estimated that 40% of them are obese. That results in approximately 18 million women at increased risk for breast cancer! This does not count those considered to be overweight, whose risk is also increased by their body weight status. Thus, a clearer understanding of the role of body weight/weight gain/body fat in the development of breast cancer and more importantly a clarification of potential mechanism(s) of action will provide valuable insights into prevention strategies.

Estrogen and Body Weight

For postmenopausal women significant increases in estrone, estradiol, and free estradiol are associated with increasing BMI (45–51). This relationship may be modified by physical activity resulting in lower serum levels of estrogens from higher levels of

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Abbreviations: AdipoR, Adiponectin receptor; BMI, body mass index; ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; MMTV, mouse mammary tumor virus; PR, progesterone receptor.

activity (47). If not considered during data analysis, this could impact interpretation of results about estrogen's relationship to body weight. Data on whether alcohol intake affects serum estrogens in postmenopausal women are not consistent. Some studies indicate that increased intake is associated with higher serum estrogens, whereas others do not indicate this response (47, 48, 50). Estradiol levels have been similar in premenopausal obese and lean women (52).

Body Fat as the Source of Estrogen

The biosynthesis of estrogens differs between premenopausal and postmenopausal women (53). Premenopausal women mainly synthesize estrogens in the ovary. However, in postmenopausal women ovarian biosynthesis is replaced by peripheral site synthesis, and in obese postmenopausal women, adipose tissue is the main source of estrogen biosynthesis. The primary mediator of postmenopausal estrogen biosynthesis is aromatase, which is actually a complex of enzymes (54) that is found in adipose tissue in the breast as well as tumor tissue itself (55). Androgens produced by the adrenal cortex and the postmenopausal ovary are converted into estrogens by aromatase (56, 57). This mechanism of estrogen production can lead to local estrogen levels in breast tumors that are as much as 10-fold higher compared with the circulation (58), although this is something that cannot routinely be measured. In addition, TNFα and IL-6 are both secreted by adipocytes and can act in either autocrine or paracrine manners to increase production of aromatase, which is directly related to increased synthesis of estrogen (59). A number of different aromatase inhibitors are currently used to control the peripheral production of estrogens in women who have had breast cancer, and additional applications for the aromatase inhibitors are being evaluated (55).

Estrogen and Breast Cancer

It was established over 15 yr ago that serum estrogen levels can account for differences in breast cancer risk, as reviewed in Ref. 60. However, because of the variable estrogen levels throughout the menstrual cycle, there are limited reports using data obtained from premenopausal women (61). Thus, the focus of the relationship between estrogens and breast cancer has been primarily on postmenopausal breast cancer. In the prospective Hormones and Diet in the Etiology of Breast Cancer study, there was no significant relationship of estrogen to postmenopausal breast cancer when evaluated by tertiles of estradiol levels; however, there was a significant mean difference when age-adjusted case *vs.* control analysis was performed (62). One metaanalysis of six prospective studies indicated that women that developed postmenopausal breast cancer had a significant approximate 15% increase of estrogens compared with those that did not develop the disease (63). A second more recent metaanalysis of nine prospective studies indicated a doubling of breast cancer risk for the highest serum estrogen levels (64). Results from the Nurses Health Study also support this relationship (65). Another study evaluating results from the Nurses Health Study indicated that postmenopausal breast cancer risk was increased in women with higher estrogen levels, particularly with respect to tumors that were classified as both estrogen receptor (ER) and progesterone receptor (PR) positive (66). A very recent update of the Nurses Health Study indicated that elevated serum estrogens were associated with the development of breast cancer, regardless of risk assessment by either the Gail or Rosner and Colditz models (67). In the European Prospective Investigation into Cancer and Nutrition study, postmenopausal women who developed breast cancer had significantly higher total and free estradiol levels than did controls in blood samples collected 3 yr before diagnosis (68). Further analysis by quintiles also showed increased risk in relationship to increasing serum estradiol levels. For an extensive review of factors that influence estrogen levels in postmenopausal women and that may impact breast cancer development, see Ref. 69.

Tumor Receptor Status

Expression and function of the ER, PR, and human epidermal growth factor receptor 2 (HER-2) appear to be linked in many breast cancers, and their expression alone or together has implications for antiestrogen therapy and breast cancer outcomes (70). There have been a number of studies to determine whether these receptors may be of particular importance for obese patients, and the results indicate a complex picture of interdependence between the receptors that may depend on premenopausal *vs.* postmenopausal status and tumor progression. There are two different forms of the ER (ERα and ERβ) (71). ERα is the receptor that is commonly reported when discussing whether a tumor is ER+ or ER− because activation of ERα leads to increased cell proliferation. ERβ also binds estrogens but is controlled by a separate gene, and its presence in breast cancer cells is associated with a favorable prognosis (72). In addition, the ratio of ERα to ERβ is higher in beast tumors in comparison to normal tissue or benign tumors (73, 74). Obesity and/or adult weight gain has primarily been associated with ERα+ tumors (28). Postmenopausal women in particular who are obese have had breast cancer that is often ERα+ (75), thus supporting the connection of obesity with elevated circulating estrogens promoting tumor development.

The PR has two main forms (PR-A and PR-B) that are derived from a single gene through the activation of two different promoters (76). Most clinical assays recognize both forms of the PR and will be referred to as PR for the purposes of this discussion. Studies have shown that BMI is positively correlated with both ER+ and PR+ tumors in postmenopausal women (34, 28). The amount of weight gained from age 18 (28) or 20 yr (78) has also been directly correlated with both ER+ and PR+ breast cancer, further implicating the ER and PR in the growth of breast cancer.

HER-2 is a growth factor receptor that plays a role in regulating cell proliferation and is associated with aggressive types of breast cancer. The combination of increasing levels of HER-2 and PR was directly correlated with BMI in postmenopausal women but inversely correlated in premenopausal women (79).

In contrast, when HER-2 expression alone was assessed, it was inversely related to BMI in postmenopausal women (80). Expression of the ER and PR may be most important during early stages of tumor development, but not in later development. Evidence to support this concept is that large tumors are more likely to be ER− and PR− (34). In addition, patients who are lymph node positive, *i.e.* have more advanced disease, more often have ER− and PR− tumors (81). This illustrates the complex interplay between these receptors.

Estrogen and Weight Reduction

Weight loss through either caloric restriction or gastric bypass surgery has been shown to lead to a reduction in circulating estrogens, although the relationship of the amount of weight lost to reductions in serum estrogens was not always proportional. For example, calorie restriction resulting in intakes of 1200 kcal/d using the American Heart Association step 2 diet for an average of 13.9 months resulted in an average weight loss of 14.5 kg (−15.6% of initial body weight) for postmenopausal women, whereas serum estradiol was reduced from an initial average of 25.5 to 17.9 pg/ml (82). In another study, weight reduction of 4% was associated with an 18% decrease of estradiol. This was not significant in women 50–65 yr of age, but there was a significant increase in SHBG (83).

A study of women with a mean age of 43.9 yr who had undergone Roux-en-Y gastric bypass surgery found that an average weight loss of 38.5 kg was accompanied by a decrease in estradiol from 53.9–35.7 pg/ml as well as a decrease in estrone from 69.6–48.1 pg/ml (84). Younger women with a mean age of 34.7 yr who underwent vertical banded gastroplasty lost 59 kg (percentage of body weight was not reported) 12 months after the procedure, whereas their serum levels of estradiol decreased from 94.85–73.62 pg/ml over the same period (85). Because many breast tumors in postmenopausal women are dependent on estrogen for growth, it seems likely that weight loss and the concomitant reduction in estrogen levels should lead to a reduction in breast tumor growth. In fact, a recently published paper supports this indicating that the incidence of breast cancer was reduced by 85% after gastric bypass surgery (86).

Preclinical Studies

In agreement with human studies, an increased incidence of spontaneous and chemically induced mammary tumors has been reported for obese and overweight rodents (87–92). Additional studies have shown leanness to protect dogs from spontaneous mammary development (93), whereas overweight is associated with an increased canine mammary tumor incidence (94).

In more recent studies, the effect of body weight on the development of mammary tumors in several transgenic mouse strains has been determined. For example, dietary induced obesity was reported to be associated with shortened mammary tumor latency in transgenic mouse mammary tumor virus (MMTV)-TGF-α mice (95, 96), but not in MMTV-neu mice (97). MMTV-TGF-α mice develop tumors later in life that are considered to be hormone responsive. In contrast, the MMTV-neu mice develop ER− tumors (98). These findings are consistent with human studies cited previously, suggesting that obesity is more likely to be associated with the development of ER+ and/or hormone-responsive breast cancers.

There are few reports of the direct effect of estrogen in relationship to obesity and mammary tumor development in preclinical models. There is one paper published in 1966 that reported that when ovariectomized C3H mice, a strain of mice with a high incidence of spontaneous mammary tumors, were made obese by gold thioglucose injections, they had a decreased incidence of spontaneous mammary tumors, *i.e.* 6%, compared with an incidence rate of 44% for intact obese mice (99). Interestingly, no tumors appeared in normal weight ovariectomized mice, which was interpreted that there was a direct effect of caloric intake or obesity *per se* independent of estrogen on mammary tumor development. More recently, we attempted to investigate affects of gold thioglucose-induced obesity on the development of tumors from ER+ T47-D human breast cancer cells in a xenograft model (100). This study produced surprising results because we found in the first experiment that estrogen supplementation in ovariectomized obese mice resulted in no tumors being detected. In a second study that included both estrogen-supplemented and placebo groups, 100% tumor incidence was found in the obese placebo group compared with 50% in the nonobese placebo group, whereas, again, there were no tumors in the obese mice supplemented with estrogen. Analyses of the tumors that formed indicated that neither ERα nor ERβ was detected. In another study we investigated the effects of dietary induced obesity on tumor development from ER+ MCF-7 *vs.* ER− MDA-MB-231 human breast cancer cells (101). As expected there was little effect of body weight on tumor growth from the ER− MDA-MB-231 cells. Unfortunately, overall growth of the MCF-7 cells was not very robust, and it was not possible to determine any effects of body weight on ER+ tumor development.

Obesity-Related Factors that May Interact with Estrogen to Impact Breast Cancer

Obesity is associated with a number of additional circulating factors that may work independently as well as in concert with estrogen to impact breast cancer development. Most of the supporting evidence for these interactions results from *in vitro* studies in relationship to the ER status of human breast cancer cell lines. For example, insulin and IGF-I have had various effects on estrogen signaling in breast cancer cell lines, as reviewed in Ref. 53. There is increasing evidence that leptin, an adipose tissue-derived protein, which is positively associated with BMI and body fat, has different effects on ER+ and ER− human breast cancer cell lines. ER+ MCF-7 and T47-D cells express high levels of the leptin receptor signaling isoform, ObRl/Rb, whereas the shorter forms are present in ER− MDA-MB-231 and MDA-MB-435 cell lines (102). In addition, leptin receptor and ERα are coexpressed in breast cancer cell lines. In ER+ T47-D breast cancer cells, leptin induced cellular transformation (anchorage-

independent growth) that was not observed in normal breast epithelial cells (103). In this and other ER+ breast cancer cell lines, the addition of leptin increases cell proliferation (103–107). Of particular interest to the focus of this review, it has been found that leptin modulates estrogen synthesis and ERα activity by up-regulation of aromatase gene expression and aromatase activity in MCF-7 cells, leading to increased estrogen synthesis (108).

Another adipose tissue-derived protein is adiponectin, which is reported to be inversely related with body weight/body fat. Receptors for adiponectin, adiponectin receptor (AdipoR) 1 and AdipoR2, are expressed in both ER+ and ER− human breast cancer cell lines (109–112). A recent study from our laboratory has shown that MCF-7, MDA-MB-231, MDA-MB-361, T47-D, and SKBR3 cells not only express AdipoR1 and AdipoR2, but also adiponectin itself (112). Of further interest, addition of adiponectin to different human breast cancer cell lines inhibited proliferation (109, 111, 112, 77). When comparisons of different human breast cancer cell lines were made, adiponectin inhibited the proliferation of the ER− SK-BR-3 breast cancer cell line at a higher concentration than it inhibited ER+ MCF-7 and T47-D breast cancer cell lines (112) (44). This suggests an estrogen and adiponectin interaction. Adiponectin may also enhance aspects of apoptosis signaling in breast cancer cells (111, 112), although one study showed no role of apoptosis in the inhibitory effect of adiponectin on T47-D cell proliferation (109).

Conclusions

It is now well established that obesity is a risk factor for postmenopausal breast cancer, particularly the development of hormone-responsive tumors. Elevated circulating estrogen levels as well as local production of this hormone have been implicated as a primary growth factor in this relationship. In addition, adipokines directly synthesized in adipose tissue may influence mammary tumorigenesis by impacting both circulating and locally produced levels of these proteins. Continuing research will determine whether these factors work independently and/or in concert with each other. Prevention of adult-onset obesity should be a major public health goal to delay or prevent some kinds of breast cancer.

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