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The Relationship between Obesity and Breast Cancer Risk and Mortality

Obesity is an established risk factor for postmenopausal, but not premenopausal, development of breast cancer. Evidence for a positive association between obesity and breast cancer mortality is mounting. Avoiding adult weight gain and maintaining a healthy body weight may contribute importantly to decreasing breast cancer risk and mortality, especially in postmenopausal women.

Key Words: obesity, BMI, breast cancer risk, breast cancer mortality

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Obesity is an established risk factor for breast cancer in postmenopausal women,[1] but not in premenopausal women.[2] Few studies have assessed the relationship between obesity and breast cancer mortality. Obesity has been shown to increase breast cancer mortality in women after menopause in the Nurses' Health Study by Huang et al.[3] and in a large Norwegian study by Tretli.[4] The recently published study in *Cancer Causes and Control* by Petrelli et al.[5] strongly supports these findings. The authors showed that breast cancer mortality rates increased continually and substantially with increasing body mass index (BMI, kg/m^2) in postmenopausal women (relative risk [RR] = 3.08, 95% confidence interval [CI] = 2.09–4.51 for BMI ≥40 compared with BMI 18.5–20.49 [p for trend <0.0001]). The authors used a sample of 424,168 eligible women who were postmenopausal and cancer-free at baseline. These women were selected from 676,306 female participants in the Cancer Prevention Study II, a prospective mortality study of American men and women begun by the American Cancer Society in 1982. After 14 years of follow-up, 2,852 breast cancer deaths were observed. Cox proportional hazards modeling was used to estimate relative risk and to control for potential confounders such

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as age, height, race, a history of breast cancer in a mother or a sister, a personal history of breast cysts, age at first live birth, parity, age at menarche, age at menopause, menopausal type (natural, surgical, unknown), use of estrogen replacement therapy, years of education, smoking status, total physical activity level at work or play, and alcohol intake. This finding was important because it not only supported previous positive findings, but also showed a stronger association between BMI and postmenopausal mortality than had been reported previously.

The association between obesity and breast cancer mortality may be attributed to comorbidity issues that come with increased obesity. The evidence for the relationship of obesity to a number of comorbidities such as diabetes, hypertension, cardiovascular disease, gall bladder disease, and some cancers is strong.[6] In addition, higher frequency of large tumors, lymph node metastases, and poorer prognosis in obese compared with lean breast cancer patients have been observed.[7] Obese women with breast cancer have been found to have decreased survival rates and increased recurrence.[5] According to Petrelli et al.,[5] the higher death rate found in their study may be due to a true biologic effect of obesity or to delayed diagnosis in heavier women. Endogenous estrogen levels in postmenopausal women, which are 50 to 100% higher among heavy than in leaner women, are produced primarily in the adipose tissue.[3] Estradiol levels in postmenopausal women have been reported to increase with increasing BMI.[8] In addition, the level of unbound or loosely bound biologically available estrogen is higher in obese than in lean women because sex hormone–binding globulin level is lower in obese women.[3,9] Estrogen-sensitive tissues in obese women are therefore exposed to more stimulation, which leads to more rapid growth of metastatic tissues, than those of leaner women.[3,9] Breast cancer is also more likely to be detected later in the disease in obese women.[1] This is because detection of the breast tumor is more difficult in obese than in lean women.[1,3,5] Late-stage tumors have been associated with poor prognosis.[1]

In the study by Huang et al.,[3] current BMI and weight gain were strongly associated with fatal postmenopausal breast cancer. The multivariate RRs were 1.90 (95% CI, 1.26–2.88) for current BMI >28 compared with a BMI ≤21, and 2.44 (95% CI, 1.40–4.25) for weight gain >20 kg compared with weight change ≤2 kg. However, the association between BMI and postmenopausal breast cancer mortality was stronger among women who never used exogenous postmenopausal hormones (RR = 2.17 [95% CI, 1.23–3.82] for BMI >28 compared with BMI ≤21). A weight gain of >20 kg compared with a weight change ≤2 kg since age 18 was also strongly associated with breast cancer mortality in postmenopausal non–hormone users in that study (RR = 3.80 [95% CI, 1.61–8.97]). Findings tended to be stronger in non–hormone users because use of exogenous postmenopausal hormones elevate estrogen levels even among lean women. According to Huang et al.,[3] the effect of obesity on breast cancer mortality was attenuated in that study because the pharmacologic levels of exogenous estrogens are generally greater than those owing to obesity.

Postmenopausal women with relatively high serum concentrations of total estradiol, free estradiol, estrone, estrone sulfate, and androgens such as testosterone had approximately a twofold higher risk of breast cancer than those with low levels.[10] These recent findings by The Endogenous Hormones and Breast Cancer Collaborative Group support the long-hypothesized role of endogenous hormones, especially estrogens, in the etiology of breast cancer.[10] In addition to obesity in postmenopausal women, many of the established risk factors of breast cancer such as age at menarche, age at menopause, and parity, are hormone related. Many studies reported a protective relationship between obesity and premenopausal breast cancer risk.[1,3] An increased frequency of anovulation in obese premenopausal women, which has been shown to reduce serum estradiol and progesterone levels, may partially explain the reduced risk observed in many studies.[3,11] Unlike in postmenopausal women, the amount of additional estrogen exposure from peripheral conversion of androstenedione to estrone in adipose owing to obesity may be less consequential in premenopausal women in whom cyclic hormone levels predominate.[11] Reduced breast cancer risk may also be due to increased leptin levels in fat stores of obese young women; leptin inhibits ovarian estrogen production.[11] Further, premenopausal breast cancer risk may be lowered in obesity as a result of increased parity, a factor that is protective.[5,12]

Findings on obesity and premenopausal breast cancer risk, however, are still inconclusive. Previous studies have also reported negative or no association between BMI and breast cancer risk in premenopausal women.[2,13] Body fat distribution may be an important confounder in studies examining the relationship between premenopausal breast cancer risk and obesity.[13] Many previous studies did not control for body fat distribution.[13] Our data on sex hormonal profile of premenopausal white women suggest that women with normal body fat distribution (0.75 < waist-to-hip ratio [WHR] ≤ 0.80) may have a hormonal pattern that is more protective of breast cancer than women with lower body fat distribution (WHR ≤0.75).[13] Data were analyzed controlling for BMI and other risk factors of breast cancer.

Body fat distribution may be a better marker for breast cancer risk than degree of adiposity in both pre- and postmenopausal women.[14,15] Upper body adiposity

has been hypothesized to be a more specific marker of a premalignant hormonal pattern than degree of adiposity.[14] Our recently published work on premenopausal African American women supports this hypothesis.[15] Our findings also suggest that obese upper body fat–phenotype African American (BMI >27 and WHR >0.80) women, in particular, have a high-risk hormonal profile. Indeed, in the study of African American and white women (aged 20 to 74 years) by Moorman et al.,[9] those who were severely obese (BMI ≥32.3) and had a WHR in the highest tertile (WHR ≥0.86) were more likely to be diagnosed with later-stage breast cancer. The odds ratio for women who were both severely obese and were in the highest WHR tertile was 3.61 (95% CI, 2.02–6.43) compared with the reference category that was in the lowest WHR tertile (WHR ≤0.77) and that were not severely obese (BMI <27.3). In addition, inclusion in an age-adjusted model of WHR explained 20%, and inclusion in an age-adjusted model of both WHR and severe obesity explained 27%, of the later stage at diagnosis in African American women. These findings suggest that obesity and upper body adiposity contribute substantially to the relation between race and stage at diagnosis.[9]

In addition to having a premalignant sex hormonal profile, obese women with upper body adiposity tend to have more visceral fat, which can lead to various metabolic disorders such as glucose intolerance, insulin resistance, hyperinsulinemia, and hypertriglyceridemia.[16] Abdominal obesity is also often associated with increased levels of insulin-like growth factor type 1 (IGF-1).[9] Both insulin and IGF-1 have been shown to have mitogenic activity in mammary cancer cells, and IGF-1 may act synergistically with estrogen to stimulate growth of breast cancer cells.[9]

One would expect both pre- and postmenopausal African American women to have higher breast cancer incidence and mortality rates compared with white women. This is because higher prevalence of obesity and upper body adiposity have been observed in African American compared with white women.[9,11,15] In both pre- and postmenopausal women, the breast cancer mortality rates are indeed higher in African American than in white women.[17] Whereas the premenopausal breast cancer incidence statistics indicate a slightly but consistently greater rate in African American women than in white women, however, the incidence rate in postmenopausal women is lower in African American than in white women.[17] Racial differences in breast cancer survival and mortality rates have been attributed to a number of factors, such as access to medical care and socioeconomic factors, with later-stage diagnosis being a major reason.[9,11] In a population-based case-control study of 20- to 74-year-old African American and white women from North Carolina in 1993–1996, Hall et al.[11] found that among premenopausal women, BMI was inversely associated with breast cancer risk for white but not for African American women. No association between BMI and breast cancer risk among postmenopausal women was found. When analyses were restricted to women ≥50 years old who had never used hormone replacement therapy, however, a strong BMI–breast cancer association was observed in white women, but not in African American women. Hall et al.[11] speculated that in African American women, the absence of an inverse association between BMI and premenopausal breast cancer, and the lack of an association between BMI and postmenopausal breast cancer, may be related to the high rate of surgical menopause in their study population (27% of their young African American study subjects reported hysterectomy with oophorectomy). The authors also speculated that the absence of a BMI–breast cancer association in postmenopausal African American women may be related to their high prevalence of estrogen receptor–negative breast tumors. These tumors are unlikely to be responsive to the increased estrogen stimulation caused by obesity.

African American women have less visceral fat or metabolically active fat, and have more subcutaneous fat compared with white women of similar age, WHR, and BMI.[18] This may be yet another factor accounting for the differences in the obesity–breast cancer incidence and mortality rates observed in pre- and postmenopausal African American and white women.

The relationship between obesity and breast cancer incidence and mortality is complex and especially difficult to interpret. Nevertheless, enough evidence, especially in postmenopausal women, exists to support a potential benefit to maintaining a healthy body weight and preventing adult weight gain so as to reduce breast cancer risk and deaths. In the study by Petrelli et al.,[5] the proportion of breast cancer deaths attributable to overweight and obesity in the general U.S. postmenopausal female population was approximately 30 to 50%, depending on whether lean or normal-weight women were used as the referent group for RR estimates. This was based on the assumption that BMI in adulthood, measured within the 14-year period prior to death, was causally associated with breast cancer. Using the U.S. 1988–1994 population data on prevalence of overweight (BMI ≥25) and obesity (BMI ≥30) in women aged 50 to 69 years, which exceeded 64% and 32%, respectively, the authors estimated that 11,000 to 18,000 deaths per year from breast cancer in U.S. women above 50 years of age might be avoided if women could maintain a BMI <25 throughout their adult lives.[5] As the authors indicated, the public health significance of these estimates is profound. Few risk factors of breast cancer are modifi-

able. Because body weight is modifiable through proper diet and physical activity, weight control provides an important opportunity to decrease breast cancer risk and mortality, especially in postmenopausal women.

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Moderate Changes in Weight and Physical Activity Can Prevent or Delay the Development of Type 2 Diabetes Mellitus in Susceptible Individuals

The prevalence of type 2 diabetes mellitus is rising significantly, paralleling the increase in obesity observed around the world. Diabetes is a progressive disease that frequently results in serious complications including retinopathy, neuropathy, nephropathy, and cardiovascular disease. Early detection and treatment of hyperglycemia, the cornerstone of diabetes, can decrease the incidence of these sequelae. Moderate changes in both body weight and physical activity improve the control of hyperglycemia associated with diabetes. Recent studies indicate that similar lifestyle changes can help to prevent or delay the onset of diabetes in people at risk of developing this disorder.

Key Words: type 2 diabetes, lifestyle, diet, exercise, physical activity, weight loss

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Type 2 diabetes mellitus, formerly known as adult-onset diabetes or noninsulin-dependent diabetes, affects ap-