Breast Cancer Prognosis: Weighing the Evidence on Weight and Physical Activity

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Traditionally host factors such as weight and physical activity have not been considered in the overall treatment of breast cancer patients. In this issue of ONCOLOGY, Nagaiah and Abraham review the epidemiologic and biologic evidence evaluating the relationships among obesity, physical activity, and both breast cancer recurrence and mortality, and in doing so, advocate weight management and exercise for breast cancer patients.

Body Mass Index

Body mass index (BMI), calculated as weight (kg) divided by squared height (m²), is currently the most commonly used measurement of obesity in both epidemiologic and clinical studies. Based on World Health Organization categorizations, a BMI ≥ 25 kg/m² is considered overweight and ≥ 30 kg/m² is obese. However, these cutoffs are likely to vary for some racial/ethnic groups. Being overweight or obese is an established risk factor for postmenopausal breast cancer, particularly the hormone receptor–positive phenotype.[1] Increased estrogen production resulting from the peripheral conversion of estrogen by aromatase in adipose tissue is believed to be an important etiologic factor in this relationship.[2] Growing evidence links obesity to breast cancer recurrence and mortality. Nagaiah and Abraham highlight seven studies examining obesity and breast cancer recurrence and/or mortality,[3-9] and we have identified five additional studies.[10-14] The majority of these studies observed a positive association between obesity and overall mortality, with estimates ranging from a 10% to 65% increase in mortality for obese women. Several studies also found modest positive associations between obesity and breast cancer–specific mortality, disease-free survival, and recurrence.

As suggested by the authors, the underlying biologic mechanisms are still to be elucidated. In addition to an increase in the peripheral conversion of androgens to estrogens in adipose tissue, perturbations in glucose, insulin, and insulin-like growth factor (IGF-1) levels, along with alterations in sex hormone–binding globulin, as well as adipokines such as leptin and adiponectin, and inflammation are believed to play a role. These factors may also be influenced by physical activity, which makes it hard to separate the effects of weight from physical activity.

Some evidence suggests that obese women are more likely to be diagnosed with larger, higher-grade, and hormone receptor–negative tumors.[3] This could be biologic and/or due to differences in screening practices and limitations of screening devices in this group.[15,16] However this is unlikely to completely explain the positive association between obesity and mortality, since most studies have adjusted for stage at diagnosis and tumor size. Differences in study design, including timing of obesity measurements, as well as differences in tumor phenotype, comorbidities, treatment, and other prognostic factors may explain some of the reported inconsistencies among studies.

Timing of BMI Measurement

Most studies have focused on BMI at or near diagnosis, though some have considered BMI at 1 year or more prior to diagnosis. The availability of repeated measures of BMI prior to and postdiagnosis would be ideal, but such information can be difficult to obtain. BMI measured at diagnosis may represent tumor or treatment-related effects, which tend to be transient and therefore less likely to significantly affect breast cancer mortality, whereas obesity measured 1 to 5 years prior to diagnosis or postdiagnosis may be more representative of a woman’s average body weight. A few studies have
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looked at the effect of weight change on breast cancer mortality with mixed results [9-11].

Other Factors That May Impact Breast Cancer Outcomes in Obese Women

In addition, factors such as age, smoking, hormone receptor status, menopausal status, and use of hormone therapy (HT) may modify the association between BMI and breast cancer outcomes and should be taken into consideration in analyses. The Nurses Health Study observed that BMI prior to diagnosis was strongly associated with breast cancer mortality in “never-smokers” and premenopausal women, but not in smokers or postmenopausal women.[10] In addition, a study of postmenopausal breast cancer patients found that obese women who had ever used HT prior to diagnosis had a two-fold increased risk of breast cancer mortality, while obese “never-users” were not at increased risk.[14] So far, studies have not been consistent in collecting or examining these factors. Comorbid conditions prevalent in obese women, such as diabetes, may also affect both overall survival and breast cancer mortality.[17] Furthermore, obese women may not receive the same treatment as non-obese women due to concerns about side effects, which may have an impact on survival.[3]

Physical Activity

Like obesity, decreased physical activity has been consistently associated with breast cancer incidence, but fewer studies have considered its effect on breast cancer recurrence and prognosis.[18] The authors cite three studies of physical activity, recurrence, and mortality,[19-21] and we noted five additional studies that have recently been published.[22-26] Many studies found inverse associations between physical activity and all-cause mortality, but there is less evidence for breast cancer mortality and very little evidence on recurrence. Similar to considerations that arise when studying obesity, the concepts of when to measure physical activity and how physical activity interacts with host factors are important issues. Though all the studies reviewed used metabolic equivalent task hours (METs) to quantify physical activity, some studies measured lifetime physical activity, whereas others focused on physical activity prior to diagnosis or following diagnosis and treatment. In addition, some studies considered total activity, while others measured recreational, occupational, and household activity. Studies that report lifetime physical activity rely on participants’ self-report of past activity, which may lead to biased effect estimates. It is unclear to what extent observed beneficial effects of physical activity depend on body weight or weight loss. Some studies found similar effects of physical activity regardless of BMI,[20,21,23] while others found that physical activity reduced mortality only in overweight and obese women.[19,24,25] In addition, associations among physical activity, recurrence, and mortality may not be causal, but rather reflect underlying disease severity, particularly when physical activity is measured near diagnosis and/or treatment. This could result in an observed protective effect between physical activity and recurrence/mortality—a case of reverse causation. A greater understanding of the underlying biology will help tease out these associations.

Conclusions

In summary, there is enough evidence to support the integration of weight management and physical activity into the clinical care of breast cancer patients, particularly those who are overweight or obese. Well designed epidemiologic studies and intervention trials should focus on evaluating measures of adiposity prior to diagnosis, postdiagnosis, and following treatment in parallel with mechanistic studies to further increase our understanding of the underlying biology. Understanding how host factors interact with obesity would aid in the counseling of patients as well as in targeting obesity interventions to specific groups of breast cancer patients.

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References:

References


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