

THE ROLE OF OBESITY IN THE SURVIVAL OF BREAST CANCER PATIENTS

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Breast cancer is a major cause of female mortality, with over 521,000 world wide deaths reported annually. It is the most common form of cancer in women, accounting for more than a quarter of all malignancies diagnosed in females. The association between increased adiposity and cancer is related to the hyper-insulinemia induced by the higher number and volume of the adipocytes. For the same reason, the cancer is associated with type 2 diabetes where is supplementary cancerigenic impulse can be induced by oral treatment (such is sulphonylurea drugs).

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INTRODUCTION

Breast cancer and obesity has been consistently shown to increase rates of breast cancer in postmenopausal women by 30 to 50% but in premenopausal women there is an inverse relationship. Adiposity located centrally is an independent predictor factor of postmenopausal breast cancer risk beyond the risk attributed to overweight alone. Both BMI and weight gain are more strongly related to risk of breast cancer among postmenopausal women who have never used hormone replacement therapy, compared with women who have used hormones. These results support the hypothesis that adiposity increases breast cancer risk through its estrogenic effects. Studies of breast cancer mortality and survival among breast cancer cases illustrate that adiposity is associated with both increased likelihood of recurrence and reduced likelihood of survival among those with the disease, regardless of menopausal status and after adjustment for stage and treatment. It was observed that adiposity is associated with a more aggressive tumor; obese women are more likely than lean women to have increased tumor size, lymph node involvement, and later stage disease at diagnosis.

OBESITY AND BREAST CANCER PROGNOSIS

Numerous observational studies have examined the association between obesity at diagnosis and BC-specific and all-cause mortality. A recent systematic review and meta-analysis of 82 studies found that, compared with women who were normal weight at diagnosis, obese women were 35% more likely to die of breast cancer, and 41% more likely to die of any cause¹. The relative risks for overweight women compared to normal weight women were also significantly elevated, although to a much smaller degree (7% increased risk for BC-specific mortality and 11% increased all-cause mortality). There was evidence of a J-shaped association between BMI at diagnosis and overall mortality, suggesting that underweight women are at slightly greater risk of death compared to normal weight women. In contrast, the relationship between BMI at diagnosis and breast cancer-specific mortality was linear, with no significant increase in risk at the lower end of the BMI scale. There was clear evidence of a dose-response relationship between increasing BMI and increasing risk of both breast cancer-specific and all-cause mortality, when underweight women were excluded; for both outcomes, each 5 kg/m² increase in BMI was associated with a 17% increased risk for overall

mortality and an 18% increased risk for breast cancer specific mortality.

An important consideration is that there was substantial heterogeneity across the study populations and designs included in this meta-analysis. Eleven studies were follow-up analyses from randomized clinical trials, where participants were selected on variables such as menopausal status, ER status and/or nodal status by design¹⁻¹⁰. Most of the observational studies included premenopausal and postmenopausal women together, or women with ER+ and ER- disease, although the majority did not stratify by menopausal or receptor status in examining associations between obesity and mortality. This is significant because studies conducted exclusively in one subtype versus another show discordant results, suggesting the effect of obesity on breast cancer mortality may be modified by subtype. In addition, most of the studies to date have been conducted in majority non-Hispanic white women.

RELATIONSHIP BETWEEN HORMONE RECEPTOR STATUS, MENOPAUSAL STATUS AND OBESITY

A 2012 meta-analysis combined hazard ratios (HR) for 21 studies that explicitly examined the association between obesity and breast cancer-specific mortality and overall mortality by ER status, and/or menopausal status¹¹. The meta-analysis found that for all groups (ER+, ER-, premenopausal and postmenopausal), obesity was significantly associated with increased overall mortality. Notably, the association between obesity and breast cancer specific mortality was not statistically significant among premenopausal women (pooled HR 1.18 [95% CI 0.82-1.70]), but was significant for postmenopausal women, women with ER positive disease, and borderline significant for women with ER negative disease (pooled HR 1.46 [95% CI 0.98-2.19]). Although the pooled HR for obesity and overall mortality for ER+ disease was somewhat higher than that for ER- disease (1.31 [1.17-1.46] vs. 1.18 [1.06-1.31]), there was no statistically significant interaction. Similarly, the pooled HR for obesity and overall mortality was slightly greater in premenopausal (1.23, 1.07-1.42) than in postmenopausal women (1.15, 1.06-1.26), these differences were not statistically significant. Estimates for additional subgroups, such as by race, or for combinations of menopausal status and ER status (i.e. ER+ premenopausal women) were not

available or included. Few studies have been conducted in women with triple negative disease, and findings among this group have been largely null^{2, 12}. One reason for these findings could be lack of power – most studies have small numbers of women with triple negative breast cancer, although Dawood *et al.* studied 2300 women with triple negative disease and found null results¹³. Another possible issue is that women with triple negative disease have relatively high mortality rates overall, and so detecting a difference across BMI categories may be difficult. Finally, it is possible that results would differ by menopausal status in these women. Only one study, conducted among 1100 Chinese women, has stratified analyses in triple negative women by menopausal status, and they found that only premenopausal women were at greater risk for breast cancer mortality if they were overweight compared to lean women¹⁴. Results were null among postmenopausal women.

PREVALENCE OF OBESITY BY RACE

Although it is well recognized that the prevalence of overweight and obesity is steadily increasing over time in the US and other developed countries, black women in particular are the most disproportionately affected group. In the latest analysis of the National Health and Nutrition Examination Survey (2011–2012), the age-adjusted prevalence of overweight (BMI ≥ 25 kg/m²) was 82.0% among non-Hispanic black women versus 63.2% among non-Hispanic white women¹⁵. The prevalence of obesity was 56.6% in black women, compared to 32.2% in white women, and 16.4% of black women were morbidly obese (BMI ≥ 40 kg/m²) compared to 7.4% of white women. As discussed above, black women are also more likely to die of BC than white women, and black women still experience a survival disadvantage compared to whites even when restricted to women with stage I tumors. These findings have led some to hypothesize that obesity at BC diagnosis may mediate the association between black race and poor survival in women with BC. Three studies have explicitly examined the association between obesity and mortality in black and white BC survivors by race¹⁶⁻¹⁸. Two of these studies^{16, 17} were incorporated into the pooled analysis¹⁸. One of these studies was conducted among postmenopausal women in the Multiethnic Cohort study, and found that pre-diagnostic obesity was significantly associated with increased all-cause and BC-specific mortality overall, although

being overweight was not¹⁷. In analyses stratified by race/ethnicity, the increased risk remained significant only for Caucasian women, although trends for increased risk with obesity were observed across the other ethnic groups. The study was limited by missing ER status in 31% of cases and lack of information on comorbidities. Lu *et al.* evaluated the association between obesity (as measured by BMI 5 years prior to diagnosis) and survival among black and white women with invasive BC aged 35–64 years¹⁶. In this study, black women overall were significantly more likely to die of BC or any cause. Obesity as measured 5 years prior to diagnosis was associated with increased risk for both BC-specific and all-cause mortality overall. In estimates stratified by race, obesity was significantly associated with both BC-specific and all-cause mortality among white women; estimates among black women were null. Further, the trends for black women and white women were statistically significantly different from one another. In a mediation analysis, the authors found that BMI did not mediate the association between black race and increased mortality, after adjustment for age, education, tumor characteristics, study site, and comorbidity.

Finally, Kwan *et al.* (2014) performed an analysis of prediagnostic body size and mortality by race/ethnicity in BC survivors from the California Breast Cancer Survivorship Consortium, a pooled study of 3 population-based case-control studies and 3 prospective cohort studies¹⁸. BMI was derived from self-reported or measured weight and height at least 6 months prior to BC diagnosis (up to a mean of 5 years prior to diagnosis for 3 of the 6 studies). They found that survivors who were underweight (BMI < 18.5 kg/m²) or morbidly obese (BMI ≥ 40 kg/m²) had significantly greater risk of both BC-specific and all-cause mortality compared to normal weight survivors overall. However, there was no significantly increased risk of death associated with intermediate categories of BMI (overweight, obesity, or severe obesity). Upon stratification by race/ethnicity, similar associations were observed among the non-Latina white women and Latinas, but not among African-American women, for whom there was no association between any level of overweight/obesity and mortality. Stratification by ER/PR status did not reveal statistically significant interactions of BMI and breast cancer-specific mortality, although the number of outcomes in some categories was small. Further, no significant interactions were found by menopausal status, or by hormone receptor and menopausal status within

race/ethnic groups. Although this study was large (over 11,000 women), multiple stratifications resulted in some lack of power to detect associations. Further limitations of this study included missing ER/PR status on 15% of cases, the lag time between BMI ascertainment and breast cancer diagnosis, and lack of details on treatment, such as dose and duration.

Notably, the proportion of black women who were obese in these three studies was substantially lower than what is currently seen in the general US population. While 56% of non-Hispanic black women in the US were obese, according to 2011–2012 estimates, the prevalence of obesity among black women in these cohorts ranged from 27%¹⁶ to just below 40%^{17, 18}. Although these studies took place in cohorts that were assembled in the 1990s and 2000s, prevalence of obesity and overweight in the non-Hispanic black population during 1999–2010 in the general population was just as high as what has been seen more recently¹⁹. Therefore, these previous studies may not be generalizable to the growing population of overweight and obese women, particularly black women.

WEIGHT GAIN IN BREAST CANCER SURVIVORS

Numerous studies have reported on weight gain in breast cancer survivors post diagnosis. Most of these studies have been comprised exclusively of survivors, with no comparison to controls. Almost all survivor-only studies have reported an increase in weight (ranging from 0.1 to 10 kilograms) over time (from 6 months to 7 years)²⁰. Some, although not all, studies found that receipt of chemotherapy, and younger age and/or premenopausal status at diagnosis were associated with greater weight gain among survivors. However, the variable amounts of follow-up time, as well as heterogeneity in how and when weight was measured in relation to breast cancer diagnosis, has made it difficult to compare and summarize weight changes across studies. In addition, lack of comparison to a control group has made it impossible to ascribe the weight gain observed in these studies to being a breast cancer survivor (i.e. “survivor status”) and type of treatment received, *versus* the effects of aging or undergoing menopause.

Two studies that did compare change in weight over time in breast cancer survivors to that of controls did not report a significant difference between groups. These studies both had limitations. One study had a small sample size and only 6 months follow-up²¹. The other study, while more

robust, did not perform analyses stratified by treatment in their comparison to controls²².

PROGNOSTIC IMPACT OF WEIGHT GAIN IN BREAST CANCER SURVIVORS

A number of studies have examined the relationship between post-diagnosis weight change in BC survivors and prognosis (breast cancer recurrence, breast cancer specific- or overall mortality)^{13–28}. In one prospective study of over 5000 BC survivors, increased in BMI of at least 2.0 kg/m² after diagnosis was associated with increased risk for breast cancer recurrence, BC death, and all-cause mortality, although this relationship was only observed in never-smokers¹³. Another study found some evidence of elevated risk for breast cancer recurrence and all-cause mortality only as a result of large weight loss ($\geq 10\%$) compared to survivors who remained weight stable¹⁴. This study found no association between weight gain and mortality. The association for weight loss with mortality was somewhat stronger for women who were obese at diagnosis compared to normal weight. Nichols *et al.* found that weight gain was associated with increased risk for all-cause, breast cancer-specific, and cardiovascular disease mortality, and these associations were not modified by prediagnosis BMI or smoking²⁵. Bradshaw *et al.* observed increased risk for both BC-specific and all-cause mortality for women who either lost or gained weight post-diagnosis²⁷, and another study found increase in risk for both recurrence and breast cancer mortality as a result of any weight change $> 5\%$ (combining weight losers and gainers in the same category)²⁶.

CONCLUSION

Despite numerous reports documenting weight gain in women after breast cancer, only a few studies have examined whether women with breast cancer are at greater risk for weight gain than their cancer-free peer. Therefore, it has remained unclear whether weight gain observed in breast cancer survivors is a result of cancer and its treatments, or simply the typical effects of aging and menopause

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