After malignancies of the skin, breast cancer is the most common cancer among women in North America. Breast cancer constitutes 26% of all cancers and 15% of cancer-related mortalities among women in the United States.[1] With approximately 2.5 million breast cancer survivors, many of these patients will develop either local or distant relapse of their disease.[2] It is therefore important to identify modifiable risk factors influencing disease recurrence. Diet and lifestyle changes are modifiable factors that are relatively easy to change and could affect long-term survival in breast cancer patients. Patients typically look to treating clinicians for advice regarding lifestyle changes that could improve their disease outcome. This article evaluates the impact of obesity and exercise on breast cancer relapse and mortality.

Obesity and Breast Cancer

Obesity is considered a risk factor for breast cancer. With 66% of patients being obese at diagnosis, this is slightly higher than the prevalence of obesity (60%) in the United States generally.[3] In a cohort of 3,993 women with nonmetastatic breast cancer followed for an average of 6.3 years, each 5-kg gain in weight was associated with a 13% increase in breast cancer–specific mortality ($P = .01$).[4] Postmenopausal women with a body mass index (BMI) of more than 30 kg/ m2 have a relative risk of developing breast cancer ranging from 1.23 (95% confidence interval [CI] = 1.00–1.59) to 2.52 (95% CI = 1.62–3.93).[3,5]

Risk of Death and Recurrence

In some studies, obese patients also seem to have a higher incidence of estrogen receptor (ER)-, progesterone receptor (PR)-, and HER2/neu-negative (“triple-negative”) tumors, which carry a poorer prognosis.[6-8] Chlebowski and colleagues performed a comprehensive literature review including information from 159 references, based on observational studies showing that women who are overweight or who gained weight after breast cancer diagnosis had a greater risk of breast cancer recurrence and death compared with lighter women.[9]

### TABLE 1

| Studies of Obesity and Breast Cancer Recurrence |

In a single-center study of 1,367 patients with breast cancer followed for a median duration of 6.8 years, women in the highest weight category ($\geq 175$ lb [79 kg]) experienced a 2.5-fold increased risk of dying from breast cancer (hazard ratio [HR] = 2.54; 95% CI = 1.08–6.00; trend $P = .02$), compared to women in the lowest category of weight (< 133 lb [60 kg]) at diagnosis (Table 1). Also, ER-negative women in the upper 50th percentile of weight with early-stage disease had an almost fivefold increased risk of dying (HR = 4.99; 95% CI = 2.17–11.48; $P$ for interaction = .10) compared with women in the lower 50th percentile of weight and ER-positive tumors. Patients with early-stage cancer (stage I/IIA) who weighed more than 175 lb had a hazard ratio of 2.39 (95% CI = 1.01–5.63) for death.[10]

In a study of 6,792 patients who had been randomized to International Breast Cancer Study Group trials from 1978 to 1993, Berczal and colleagues showed that patients with a normal BMI had significantly longer overall survival (OS) and disease-free survival (DFS) compared with patients in
intermediate BMI or obese categories, after adjusting for other factors.[11] In another study, obese women had poorer outcomes and lower complete response rates while being treated with adjuvant therapy compared to normal-weight women.[12]

In a recent study from M.D. Anderson Cancer Center, Dawood et al reported that patients with locally advanced breast cancer who were either obese or overweight had a worse overall survival and recurrence-free survival compared to normal-weight patients (P = .001). In this study, obese patients also had a higher incidence of visceral recurrence (liver, lung, brain) compared to normal-weight or underweight patients.[13]

Dignam and colleagues published an analysis of 3,385 patients enrolled in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial, a randomized, placebo-controlled trial of ER-positive patients on tamoxifen therapy. The authors looked for an association between obesity and breast cancer recurrence, and they found that obesity increased overall mortality but did not affect breast cancer recurrence. Tamoxifen reduced the risk of breast cancer recurrence and mortality regardless of a patient’s BMI.[14]

**Possible Mechanism for Increased Breast Cancer Mortality in Obese Patients**

One postulated mechanism for increased relapse of breast cancer in obese patients is the increased levels of bioavailable estrogen in these patients due to greater conversion of androgens to estrogen in adipose tissue (Figure 1). Obese postmenopausal woman have been shown to have increased circulating concentrations of estrone and estradiol with concomitant decreased levels of sex hormone–binding globulin, thus leading to increased bioavailable estrogen.[15-18]

Insulin and insulin-like growth factor (IGF-1) levels increase at higher BMIs.[19] Insulin resistance, leading to increased levels of IGF-1, may promote breast tumorigenesis. Higher levels of fasting insulin in one study increased the risk of recurrence and death in breast cancer patients.[20] Obese patients also have more aggressive tumors,[21] are likely to have metastatic lymph nodes,[22,23] are more likely to be ER- and PR-negative,[21,24] and tend to have a complicated surgical course.[25,26] Undertreatment of obese patients with chemotherapy has also been reported.[27,28]

**Benefit of Exercise in Patients With Breast Cancer**

**Evidence**

In an epidemiologic study done by Abrahamson et al, 1,264 patients diagnosed with breast cancer were asked about their recreational physical activity by questionnaire (Table 2). Patients with the greatest physical activity 1 year before diagnosis had a modest reduction in the hazard ratio for death (HR = 0.78, 95% CI = 0.56–1.08).[29]
Holmes and colleagues examined data from 2,987 nurses in the Nurses Health Study diagnosed with stage I, II, or III breast cancers and looked at breast cancer mortality in relation to physical activity level. The study showed that woman engaged in at least 3 metabolic equivalents (MET) of exercise per week had a relative risk of death from breast cancer of 0.80 (95% CI = 0.60–1.06), while those with 9 to 14.0 MET/wk had a relative risk of 0.50 (95% CI = 0.31–0.82). Adjusted for other risk factors, the relative risk of death from breast cancer and the risk of breast cancer recurrence was 25% to 40% lower in women with the highest level of activity, compared to women with the lowest levels of activity. Of note, most of the benefit was seen in women with moderate activity, equivalent to walking 3 to 5 hours a week at an average pace of 2 to 2.9 mph. Patients who were ER- and PR-positive appeared to benefit the most from exercise.[30]

Similar results were reported in a prospective study of breast cancer patients followed from 1998 to 2001 in the Collaborative Women's Longevity Study (CWLS). Women engaging in greater levels of activity had a significantly lower risk of dying from breast cancer (HR = 0.65, 95% CI = 0.39–1.08 for 2.8–7.9 MET-h/wk; HR = 0.59, 95% CI = 0.35–1.01 for 8.0–20.9 MET-h/wk; and HR = 0.51, 95% CI = 0.29–0.89 for ≥ 21.0 MET-h/wk; P = .05) compared to those performing less than 2.8 MET-h/wk in physical activity.[31]

Possible Mechanisms

**TAKE HOME POINTS**

- Obesity is a poor prognostic factor for patients with breast cancer.
- Weight management initiatives should be included in multidisciplinary breast cancer programs.
- Moderate-intensity exercise (equivalent to walking 3–5 h/wk at an average pace of 2–2.9 mph) as most beneficial in one study and should be encouraged in breast cancer patients.

Previous studies have shown that physical activity decreases the incidence of breast cancer.[32] Insulin and insulin-like growth factor (IGF-1) levels increase at higher BMIs.[19] Irwin et al showed that moderate-intensity aerobic exercise decreased IGF-1 and insulin growth factor–binding protein (IGFBP) levels.[33] Decrease in insulin levels could translate into less recurrence of breast cancer and better prognosis. Another mechanism by which exercise could be beneficial is via lowering of estrogen levels.[34,35] Evidence also suggests that exercise improves quality of life in breast cancer survivors.[36]

Conclusions

Obese patients are more likely to get breast cancer and also have a worse prognosis from the disease. Exercise appears to attenuate the physiologic processes that increase the incidence and mortality from breast cancer. The feasibility of increasing physical activity in patients with breast cancer has been studied, and the results are encouraging. Exercise has also been shown to decrease all-cause mortality in patients with breast cancer. This could be a reflection of the known benefits of exercise in decreasing cardiovascular mortality. With the current obesity epidemic, it is essential that oncologists discuss the beneficial effects of exercise and weight loss in improving overall survival in patients with breast cancer.

References:


