Energy Balance in Advanced Breast Cancer: Extending Beyond the Curative Setting

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Abstract: Outcomes in early-stage breast cancer, including quality of life, body composition, physical functioning, physiologic biomarkers, cancer recurrence, and mortality, are associated with body weight, diet, and physical activity. These same endpoints may also be relevant in patients with metastatic breast cancer; however, few studies have evaluated the role of energy balance in this setting. Future work is needed to determine how body weight, nutrition, and exercise or other physical activity might affect the disease course of metastatic breast cancer, and whether energy balance may be a component of beneficial supportive or therapeutic interventions for specific patient populations living with metastatic breast cancer.

Keywords
Diet, metastatic breast cancer, nutrition, obesity, physical activity, physical function

Introduction

Obesity, diet, and physical activity, together known as "energy balance," are associated with both risk and outcomes in breast cancer. In patients with early-stage disease, obesity, poor-quality diet, and inactivity are associated with an increased risk for recurrence, cancer-related mortality, and overall mortality. Interventional studies in this population have shown that increased physical activity and (to a lesser extent) weight loss improve fitness, physical function, quality of life, and other patient-reported outcomes. A large body of evidence is available supporting the importance of appropriate energy balance in early-stage breast cancer, but much less is known about its influence on disease course and other outcomes in patients living with metastatic breast cancer (MBC). Here, we review the existing evidence for the role of energy balance in MBC and suggest future work to extend lifestyle interventions and survivorship efforts to those living with metastatic disease.

Energy Balance and Outcomes in Early-Stage Breast Cancer

Observational data demonstrate a strong association between obesity (and related factors) and both risk for breast cancer and prognosis in early-stage breast cancer.[1] In a large meta-analysis including more than 210,000 individuals with early-stage breast cancer, the rate of breast cancer–specific mortality was 35% higher in women with obesity at the time of diagnosis than in women of normal weight.[2] Additionally, in several adjuvant trials, a higher body mass index (BMI) at the time of diagnosis was predictive of worse disease-free and overall survival after correction for confounding variables.[3,4] Observational evidence also suggests that weight change affects prognosis, with greater weight gain after diagnosis associated with higher rates of recurrence and all-cause mortality.[5] Observational data also link inactivity, a key contributor to the development of obesity, to breast cancer outcomes. A 2020 meta-analysis of observational studies found a 37% lower rate of breast cancer–specific mortality and a 42% lower rate of all-cause mortality in patients who had higher vs lower levels of physical activity after diagnosis, with an inverse dose-response relationship.[6]

In addition to the body of strong observational evidence linking energy balance to outcomes of early-stage breast cancer, several randomized, prospective energy balance trials have been completed or are ongoing in survivors of early-stage breast cancer. The trials demonstrate the beneficial effects of energy balance interventions on outcomes such as physical functioning, physical fitness, body composition, bone health, sleep, and quality of life in addition to reductions in fatigue, depression/anxiety, pain, and physiologic biomarkers of inflammation and insulin metabolism.[7] Numerous ongoing studies are testing the effect of weight loss and related energy balance interventions on disease outcomes in women with early-stage breast cancer, including the BWEL study (NCT02750826). To date, however, limited prospective information is available regarding the effect of weight loss or increased physical activity on cancer recurrence and mortality in this setting.

Obesity and Outcomes in Metastatic Breast Cancer

The evidence to date does not support a significant association between obesity and outcomes in MBC. Importantly, MBC is a heterogeneous disease in which the patient's disease trajectory, disease subtype, and treatment regimen likely influence any potential relationship between body weight and disease outcomes. Ligibel and colleagues previously evaluated the relationship between BMI and survival in patients participating in Cancer and Leukemia Group B (CALGB) 40502, a randomized trial of 3 different first-line taxane agents in combination with the anti-angiogenic drug bevacizumab in human epidermal growth factor receptor 2 (HER2)–negative MBC.[8] In this large phase 3 trial, 43% of patients had obesity at the time of enrollment. BMI category was not statistically significantly associated with progression-free survival (PFS) or overall survival (OS) in obese vs normal-weight patients (PFS hazard ratio [HR], 1.01; 95% CI, 0.83-1.22; OS HR, 1.03; 95% CI, 0.84-1.26). Importantly, the majority of patients in this trial had visceral disease, and the median OS after diagnosis was relatively short, at approximately 25 months.[9] Similarly, a pooled analysis of 3 Italian clinical trials of frontline chemotherapy in MBC found no association between baseline BMI category and PFS or OS.[10] A retrospective analysis of the Unicancer French data platform of 12,999 consecutive patients with a diagnosis of any subtype of MBC found that OS was worse in underweight patients (BMI <18.5 kg/m^2), whereas being overweight or obese had no effect on survival outcomes.[11] The authors pointed out that the underweight patients in this study had a higher burden of visceral metastases, and the analysis was likely affected by weight loss as a marker of disease aggressiveness and muscle wasting. Looking at specific subtypes of MBC, a large observational analysis of 729 patients receiving therapy based on pertuzumab (Perjeta, Genentech) or trastuzumab emtansine, also known as T-DM1 (Kadcyla, Genentech), for HER2-positive MBC at Italian cancer centers found no association between BMI and PFS, but it did find an increased risk for death in patients with obesity vs those without obesity.[12] In estrogen receptor–positive disease, a recent single-institution retrospective analysis of 219 patients receiving an aromatase inhibitor for MBC also found no association between dichotomous (high vs low) BMI and survival outcomes.[13]

Body Composition and Outcomes in Metastatic Breast Cancer

Growing evidence suggests that body composition may be more strongly linked to outcomes than weight or BMI alone. Biologically plausible hypotheses have been proposed as to why body composition may matter more than the limited evaluation of weight. Body weight comprises adipose and lean muscle tissue; both tissue types have a significant effect on metabolism, inflammation, and immune regulation that could in turn affect both the patient and the tumor microenvironment.[14,15] Low muscle mass is repeatedly and significantly associated with worse survival and increased dose-limiting toxicity in advanced cancers.[16,17] In meta-analyses of 7843 patients with advanced solid tumor malignancies, low muscle mass on

computed tomographic (CT) scans was associated with significantly worse OS and cancer-specific survival (OS HR, 1.44; 95% CI, 1.32-1.56; *P*<.001; cancer-specific survival HR, 1.93; 95% CI, 1.38-2.70; *P*<.001).[17] This meta-analysis notably did not include patients with breast cancer. In early-stage breast cancer, a prospective observational study of 3241 patients found that those with sarcopenia on CT scan at diagnosis had a 41% increased risk for death. Notably, BMI alone was not related to survival outcomes in this prospective analysis.[18]

In the setting of MBC, it remains unclear how body composition is related to outcomes because of limited available data and the presence of multiple potential confounders. Retrospective and observational data collected from patients receiving cytotoxic chemotherapy for MBC have found sarcopenia to be associated with higher rates of dose-limiting toxicity,[19,20] but the evidence is not consistent.[21,22] The Italian cross-sectional SCAN study, which prospectively measured body composition on CT scans and functional status by grip strength in 139 patients with MBC, found no association between sarcopenia and treatment-related adverse events. However, the authors noted that low muscle mass and poor muscle function were both prevalent in patients with MBC, with few of them receiving nutrition or physical activity interventions.[22] Even less data is available regarding the effect of body composition on prognosis in MBC. Although some small studies have suggested that lower muscle mass is associated with shorter time to progression or increased mortality,[20,21] others have not.[23] More research is needed to understand the relationship between body composition and outcomes in patients with advanced breast cancer, with particular attention to differences by breast cancer subtype, treatment plan, and disease trajectory.

Diet and Outcomes in Metastatic Breast Cancer

The relationship between diet and outcomes in MBC is poorly understood. Overall nutritional status is clearly important in MBC, both for clinical decision making and patient quality of life, but little evidence is available to guide dietary approaches in this population outside the goals of maintaining muscle mass and body weight. Observational evidence analyzing the association of dietary patterns and breast cancer mortality support following a healthful diet after a breast cancer diagnosis, but the specific effect in MBC is unknown. On the basis of existing epidemiologic and observational evidence, the World Cancer Research Fund/American Institute for Cancer Research expert report recommends that cancer survivors follow the same guidelines given for cancer prevention, which include maintaining a healthful diet to avoid body fatness and reduce risk for recurrence and mortality.[24] The report outlines suggestive evidence to support the role of nonstarchy vegetables, carotenoids, and calcium in the diet to reduce the risk for breast cancer. However, the guidelines define "survivors" as those who have completed treatment; currently, no specific guidance is available for those living with metastatic disease, and it remains unclear whether the same dietary principles apply to this population. Notably, patient-centered studies in MBC have found high rates of patient-reported nutritional problems and the desire for nutritional information for themselves and their caregivers.[25]

An important consideration for those living with MBC is ensuring adequate protein intake. Many patients with a cancer diagnosis are motivated to make lifestyle changes that often eliminate important food groups and result in nutritional deficiencies. Several observational studies have documented patient-reported decreases in the consumption of meat and general protein intake among patients following a cancer diagnosis or patients with advanced disease, including those with advanced breast cancer.[26,27] Reduced protein intake can exacerbate the muscle catabolism that occurs as a result of metastatic cancer, cancer-directed therapy, and the side effects of medication, such as nausea and anorexia. For this reason, nutritional guidelines from the European Society for Clinical Nutrition and Metabolism for patients with cancer undergoing active treatment recommend increasing protein intake to 1.2 to 2.0 g/kg of body weight per day.[28] This expert recommendation is not specific to patients with breast cancer and is based on indirect calorimetry estimates and the general needs of older adults with chronic illness. A prospective randomized trial in 506 patients with advanced cancer (7% with MBC) admitted to a hospital found that screening with the Nutrition Risk Screening (NRS) 2002 tool and personalized nutrition support, including ensuring adequate protein intake, reduced mortality after hospitalization (odds ratio, 0.57; 95% CI, 0.35-0.94) while improving patient-reported functional and quality-of-life outcomes.[29]

Ongoing clinical studies are also evaluating the feasibility and early antitumor efficacy of novel nutritional interventions—such as intermittent fasting—in patients with advanced cancers, including breast cancer. Preclinical work has suggested that intermittent periods of fasting or very low caloric intake may be effective at reducing tumor growth and metastasis while potentially improving tumor response and reducing off-target adverse effects.[30] In animal models, low-glucose conditions resulted in lower insulin-like growth factor 1 signaling and thus suppressed tumor growth. In addition, whereas the growth of normal cells is arrested without sufficient glucose, cancer cells continue to divide. Thus, cancer treatment may be more

targeted at malignant cells while sparing normal cells from toxicity; this is termed *selective stress resistance*. Multimodality energy balance interventions combining caloric restriction with exercise may have a synergistic effect on tumor metabolism and are the subject of ongoing work. Additionally, particularly in the case of novel targeted therapies that affect glucose metabolism, the effects of energy balance interventions need to be interpreted in the context of disease subtype and treatment regimen. An ongoing trial is evaluating adherence to overnight intermittent fasting and exercise in patients with MBC, with particular attention to their effect on glucose metabolism in patients receiving cyclin-dependent kinase 4/6 or phosphoinositide 3-kinase inhibitors (NCT04708860). The DREAM study is a randomized phase 2 trial of usual care vs a diet-and-exercise intervention in 50 patients with metastatic breast or gynecologic cancer receiving intravenous chemotherapy; the primary endpoint is the tumor response rate. The intervention includes intermittent fasting for 48 to 72 hours and a low-carbohydrate diet in advance of chemotherapy, with aerobic exercise performed during the chemotherapy infusion.[31]

Importance of Physical Function and Fitness in Metastatic Breast Cancer

Maintaining energy balance is important in advanced cancer, given that both cancer and cancer-directed therapy are associated with declines in the capability to conduct essential activities independently (physical function) and the ability to perform activities efficiently (physical fitness).

Beyond the established associations with poor quality of life and disability, reduced physical function and frailty are associated with reduced survival in patients who have advanced cancers, including breast cancer.[32] In a recent meta-analysis of 26 observational studies evaluating the association between objective measures of physical function and survival in advanced cancers, worse physical function was consistently associated with higher mortality rates as indicated by the short physical performance battery measurement (HR, 2.37; $P<.001$) and the 6-minute walk test distance (HR, 2.66, $P<.001$).[32] In the Women's Health Initiative observational cohort study, frailty before a diagnosis of breast cancer was associated with higher mortality rates (HR, 1.4; 95% CI, 1.26-1.55); in addition, the rate of functional decline was faster after diagnosis than before diagnosis.[33] Physical impairments are more prevalent among patients with MBC than among those who have early-stage disease, and cancer-related impairments further differ according to site of metastatic disease. In a consecutive sample of 163 patients with MBC receiving care in a community-based setting, Cheville and colleagues demonstrated that a majority of the patients (92%) reported more than one physical impairment for which evidence-based therapy interventions already exist, such as lymphedema, focal weakness, peripheral neuropathy, exertional intolerance, and myofascial dysfunction.[34] Moreover, one-third of patients reported at least 4 problems with instrumental activities of daily living, which is considered moderate physical disability. Importantly, this work also reported a failure to offer interventions to patients with MBC and physical impairments, particularly those belonging to a minority race or of low socioeconomic status. In a mixed-methods study of patients with MBC,[35] 86% reported physical problems that limited the ability to be physically active, citing primarily fatigue, painful joints and muscles, and shortness of breath. Consistent with variability in disease presentation, variability in preferences for supportive interventions was also high; however, the majority (53%) indicated an insecurity to self-manage physical functioning and a desire for an exercise program guided by a physical therapist. Several large prospective studies have found that regular monitoring of patient-reported physical function can prevent declines and ultimately even improve survival in metastatic cancer.[36] Future work will include multimodality interventions in response to patient-reported declines. For example, Nurse AMIE is a national clinical trial evaluating a technology-based supportive care platform for rural survivors of MBC, with patient-reported outcomes and programmed interventions that include exercise, guided relaxation, and cognitive behavioral therapy (NCT95221696).[37]

In addition to poor physical function, the majority of women with MBC have cardiorespiratory fitness that is below reference range,[38] which is an established predictor of poor function and increased mortality in the general population.[39] In a cross-sectional analysis by Peel and colleagues of exercise capacity measured by oxygen uptake during peak exercise (VO_{2peak}) on treadmill testing,[38] the level of fitness was lowest in women with MBC in comparisons with those who had early-stage disease and unaffected, age-matched controls. In 44% of the women with MBC, the $VO_{2\ peak}$ was less than 15.4 $mL \cdot kg^{-1} \cdot min^{-1}$, the established level for functional independence. In this analysis, the women with MBC (n=52) and a low level of cardiorespiratory fitness by VO_{2peak} had a 78% increased risk for death relative to those with MBC and a higher VO_{2peak}. Prospective studies are needed to determine the effect of physical fitness and fitness trajectories on treatment outcomes in MBC.

Physical Activity and Exercise in Metastatic Breast Cancer

Given the importance of the association between physical

function and quality-of-life and survival outcomes, it is hypothesized that activity and exercise may be beneficial to patients with MBC as behaviors that positively influence both function and fitness. Promoting exercise in patients with MBC has been complicated by the frequent presence of bone metastases and concerns over skeletal complications; however, several studies have concluded that exercise is safe and feasible for these patients. The International Bone Metastases Exercise Working Group has provided recommendations that include recent bone imaging and pre-exercise screening with an exercise professional—specifically, a physical therapist with training in exercise for patients with cancer. Although safety recommendations have been made, as they have for obesity and quality of diet, little evidence exists to support an association between physical activity and outcomes in MBC.[40] The largest prospective evaluation to date is an observational analysis of patients with MBC who participated in the CALGB 40502 trial of frontline taxane chemotherapy and completed a Nurses' Health Study Physical Activity Questionnaire at the time of study enrollment (n=492).[8] Self-reported recreational physical activity for more than 9 metabolic equivalent [MET] hours per week at baseline vs 9 or fewer hours at baseline was not statistically significantly associated with either PFS or OS (PFS HR, 0.83; 95% CI, 0.79-1.02; OS HR, 0.81; 95% CI, 0.65-1.02). Notably, 47.6% of the participants reported no or very little physical activity, and this finding correlated with worse physician-reported performance status. More comprehensive data on the physical activity trajectories of patients with MBC are needed, and it remains unknown how a change in physical activity levels may affect survival, ability to tolerate treatment, and quality of life.

Despite the large number of physical activity or exercise intervention trials in early-stage breast cancer, few trials have evaluated the feasibility or benefits of intervention in the setting of MBC. A single-arm study of a 6-month unsupervised physical activity intervention designed to increase number of steps per day in patients with newly diagnosed MBC (N=49) reported objective improvements in physical functioning and maintained muscle mass as measured on CT scan.[41] Beyond physical activity, true exercise, defined as physical activity done with a specific prescription and with the goal of improving fitness, has been evaluated in prospective randomized studies in MBC. Scott and colleagues randomly assigned 65 patients with MBC to either aerobic training or a stretching control for 12 weeks.[42] In this trial, 9 of the 33 patients (27%) in the aerobic training group discontinued the training intervention owing to disease progression, pain, or lack of motivation, and it was therefore concluded that aerobic exercise is not feasible in this population. Importantly, although the population enrolled was heterogeneous, most of the patients had visceral metastases, were receiving chemotherapy, and had received several lines of prior therapy. Similarly, Ligibel and colleagues completed a randomized trial of a partially supervised aerobic training intervention for 12 weeks vs usual care in 100 patients with MBC.[43] The exercise intervention resulted in a significant increase in minutes spent in physical activity but did not significantly improve cardiorespiratory fitness by treadmill testing or self-reported physical function. Importantly, both of these trials used intervention-centered approaches and enrolled patients with MBC regardless of disease trajectory. In a post hoc exploratory analysis of the Ligibel trial that omitted the patients receiving cytotoxic chemotherapy, dropout rates were low and a statistically significant improvement in cardiorespiratory fitness with the exercise intervention (P=.003) was noted, suggesting a different effect size on the basis of treatment phase. A recent single-arm intervention by Groen and colleagues used a patient-centered approach in which an exercise program was tailored to target the individual physical health-related goals of patients with MBC (N=55).[44] All patients were receiving chemotherapy or had self-reported poor physical function at baseline. A significant number of participants dropped out of the intervention, the majority because of disease progression. Nonetheless, 52% of the participants fully achieved their functional goals, and 85% stated that they would "definitely recommend" the program to others with MBC.

Within MBC, disease trajectories differ markedly across individuals. For example, patients with endocrine-sensitive disease and bone-only metastases typically have more indolent disease, with approximately 40% alive 10 years after diagnosis.[45] In contrast, patients with triple-negative breast cancer and visceral involvement have an average survival of approximately 18 months; some of these patients have especially chemoresistant disease that is quickly progressive.[46] For patients with acutely progressing disease, lifestyle interventions may focus on endpoints such as quality of life, prevention of functional decline, and symptom control. In those with very indolent or stable disease, energy balance interventions may target maintenance of physical function and could ultimately affect disease biology and survival outcomes, as has been demonstrated in early-stage disease. In addition to careful attention to the enrollment population, the specifics of the dose and delivery of energy balance interventions is crucial to understanding efficacy, as they are in pharmacologic therapy trials. An ongoing phase 1/2 trial called TBCRC048 is enrolling patients with newly diagnosed metastatic estrogen receptor–positive disease to study dose delivery of aerobic exercise and determine a scalable dose with early biological activity in terms of

effect on circulating tumor cells (NCT03988595). Future work will also need to be grounded in patient-centered behavioral theory to deliver interventions designed to improve fitness and function and demonstrate effect on meaningful endpoints. In the newly launched EMBody trial, which is grounded in behavioral change theory, we will be studying a multimodality exercise intervention in patients with indolent MBC whose disease has been stable for at least 12 months. Participants will be randomized to a 16-week exercise intervention consisting of motivational interviewing for physical activity behavioral change and 3 weekly 60-minute virtual training sessions for moderate-intensity aerobic, resistance, and balance exercise. The primary endpoint of this trial is cardiorespiratory fitness as measured by a Bruce ramp treadmill protocol. Secondary endpoints are objective and subjective physical function, patient-reported quality of life, body composition as measured on CT scans obtained for disease monitoring, and behavioral predictors of adherence and efficacy (NCT05468034).

"Survivorship" and Energy Balance Work Should Extend to Metastatic Breast Cancer

The definition of a cancer "survivor," according to the National Cancer Institute, is "one who remains alive and continues to function during and after overcoming a serious hardship or life-threatening disease. In cancer, a person is considered a survivor from the time of diagnosis until the end of life." Patients with MBC are breast cancer survivors, yet they often are not included in dietary or physical activity interventions and recommendations. Guidelines for physical activity and diet are available from the American Cancer Society, the American College of Sports Medicine, the National Cancer Institute, and recently the American Society of Clinical Oncology.[47] These guidelines do not specifically address patients living with metastatic disease, and they generally designate as "survivors" those patients who have completed treatment for a curable malignancy. The recently released American Society of Clinical Oncology energy balance guidelines support a discussion of exercise during curative therapy. Because evidence is insufficient to recommend specific dietary or weight changes for these patients, the guidelines call for more research in patients with metastatic disease.

Energy balance and energy balance interventions have an established significant effect in the curative setting. Nonetheless, few prospective trials have evaluated the effect of energy balance in survivors living with MBC; those that have been done have not found a convincing relationship between body composition, diet, or physical activity and outcomes. Body composition, diet, and exercise have the potential to alter not only tumor metabolism and treatment response[48,49] but also patient quality of life, physical function, and physical fitness. Heterogeneity in both patients and disease trajectories is significant in MBC. In addition, the effect of energy balance likely differs by disease subtype (hormone receptor–positive vs HER2-positive vs triple-negative disease) and also by disease volume, sites of metastatic disease, and type of treatment received. For some patients, such as those with small-volume or bone-only disease on endocrine-based therapies, energy balance may augment the treatment response and ultimately improve survival; for others, such as those with high-volume or aggressive disease on intravenous chemotherapy, energy balance interventions may have the potential to improve functional independence and decrease the symptom burden. As detailed in this review, prior studies have been limited by small sample sizes with heterogeneous populations and endpoints; future work should focus on more homogeneous groups and endpoints targeted specifically to those groups. Although clear associations between energy balance and outcomes in MBC are lacking, it is known that patients want this information. Future work should focus on involving patient advocates in discerning the most helpful interventions and engaging patients in intervention development to extend survivorship efforts to MBC.

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