Reducing the Risk of Breast Cancer Recurrence: an Evaluation of the Effects and Mechanisms of Diet and Exercise

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Abstract With recent medical advances in diagnosis and treatment, the increasing numbers of long-term survivors of breast cancer is considerable and has resulted in the expansion of scientific research to include examination of lifestyle modifications as means of prevention of recurrence, new breast cancer events, and mortality. The objective of this report is to review randomized controlled trials (RCTs) including diet and/or exercise interventions on breast cancer recurrence in women with a history of breast cancer as well as pertinent recent epidemiologic evidence. Implicated biologic mechanisms are discussed to elucidate the impact of diet and exercise on disease recurrence.

Keywords Breast cancer · Diet · Nutrition · Exercise · Physical activity · Recurrence · Obesity

Introduction

Given the recent advances in the diagnosis and treatment of breast cancer, the number of breast cancer survivors is steadily growing, with the 5-year relative survival rate of 91% and more patients living longer past diagnosis [1]. Yet, with this greater survival, the long-term effects of breast cancer and treatment-related side effects have become increasingly evident. Breast cancer survivors are at higher risk for weight gain following diagnosis regardless of menopausal status [2], and given that obesity is a risk factor for a number of adverse outcomes, including comorbid disease, recurrence or overall mortality, research has expanded to include investigations into lifestyle modifications directed towards healthy weight management. The lifestyle modifications aimed at preventing recurrence, typically defined as a relapse event at a local, regional, or distal site, have consisted of a healthful diet, nutritional supplements, regular exercise, or some combination of these components.

Though numerous reviews have been conducted on the relationship between lifestyle factors and cancer recurrence [3–6], not all have been specific to breast cancer, focused primarily on evidence from randomized controlled trials (RCTs), or discussed the physiological mechanisms underpinning lifestyle modifications in relation to breast cancer recurrence. Therefore, the purpose of this review is to summarize evidence from recent lifestyle interventions examining the role of diet, exercise, or multicomponent approaches on recurrence and mortality outcomes in breast cancer survivors. As such, this review is organized into three sections: (1) diet interventions; (2) exercise interventions; and (3) multicomponent approaches involving diet combined with exercise. Based on this body of knowledge, reasonable recommendations on diet and exercise that aim to reduce the risk of recurrence and mortality in breast cancer survivors are provided.

Diet and Risk of Breast Cancer Recurrence

Considerable evidence exists for the role of healthy eating in breast cancer prevention, while the body of support for the
effects of diet on the risk of breast cancer recurrence is rapidly growing [3]. This section will focus on diet-only interventions rather than multicomponent approaches involving both diet and exercise, which are discussed together in a later section. Data from randomized controlled trials (RCTs) involving women with breast cancer are presented in regards to two primary dietary patterns—(1) a low-fat diet and (2) a low-fat, high fruit, and vegetable diet—and the effects of soy and vitamin D intake are also discussed.

Low-Fat Diet and Risk of Breast Cancer Recurrence

Data from large observational studies have suggested an association between higher intake of dietary fat and greater risk of breast cancer recurrence, particularly in post-menopausal women [5], motivating investigations to examine the effect of low-fat dietary interventions on breast cancer recurrence. The Women’s Intervention Nutrition Study (WINS; n = 2437) was the first of two large, multicenter RCTs employing a low-fat dietary intervention to promote relapse-free survival in women with early-stage breast cancer [7]. The second large-scale RCT, the Women’s Healthy Eating and Living study (WHEL; n = 3088), incorporated a high intake of fruits and vegetables in addition to a low-fat diet [8]; hence, it will be discussed in the subsequent section. In WINS, women aged 48–79, who had completed conventional primary treatment for early-stage breast cancer including surgery, radiotherapy, tamoxifen for estrogen receptor (ER)-positive tumors, and chemotherapy for ER-negative tumors, were recruited within 1 year of diagnosis. Forty percent (n = 975) were randomized to the low-fat dietary intervention, where participants reduced the percentage of calories from fat to 15 %. Control subjects (n = 1462) received only written dietary guidelines. After a median of 60 months, only 9.8 % of women in the diet group had reported a recurrence event compared to 12.4 % of women in the control group, with a hazard ratio for relapse-free survival, defined as recurrence at any site, of 0.76 (95 % CI, 0.60 to 0.98; p = .034). As statistically significant weight loss was observed in the intervention group compared to the control group (p = .005), the dietary intervention was purported to lower the risk of recurrence through reductions in body weight. However, no statistical significance was found for an intervention effect on overall survival (HR = 0.89; 95 % CI, 0.65 to 1.21; p = .56), although a follow-up analysis reported a significant overall survival benefit in women with ER and progesterone receptor (PR) disease (7.5 vs. 18.1 % cumulative mortality, RR 0.41, p = .003, n = 362) [9].

Low-Fat Diet and Risk of Breast Cancer Recurrence: Plausible Mechanisms

The physiological basis for the relationship between a high-fat diet and breast cancer recurrence has been attributed to higher body adiposity and the modulatory effects of dietary fats on eicosanoid synthesis [10–12]. Higher adiposity is associated with adverse levels of insulin-like growth factor 1 (IGF-1), inflammatory markers and sex hormones, all of which may act to promote tumor development and growth [10]. The role of IGF-1 and its receptor IGF-1R in the progression of breast tumors has been demonstrated through multiple breast cancer models (reviewed in Belardi et al. [13•]). Though activation of IGF-1R alone is not an oncogenic event, survival of already differentiated cells is dependent on IGF-1/IGF-1R signaling, suggesting that the IGF-1 axis is an important factor in tumor progression [14]. Indeed, high expression of activated IGF-1R is related to poorer survival in breast cancer patients [15]. However, evidence is lacking on the direct relationship between circulating IGF-1 as a result of dietary intake and its effect on IGF-1 axis signaling and tumor progression.

On the other hand, more evidence is available to support the role of adiposity in the breast cancer progression. The accumulation of adipose tissue, specifically visceral fat, increases circulating levels of pro-inflammatory cytokines, including interleukin-6 (IL-6) and transforming growth factor beta (TGF-β), and the pro-inflammatory adipokine, leptin, which are secreted from the adipose tissue itself [16, 17]. Leptin in particular has been shown to promote tumor cell growth and metastases through activation of numerous signaling pathways [16]. In addition, the resulting state of chronic inflammation from the systemic induction of pro-inflammatory cytokines has been shown to contribute to tumor angiogenesis and change to a metastatic phenotype [17–19]. For example, both IL-6 [19] and TGF-β [17] induce epithelial-to-mesenchymal transition, a correlate of late-stage tumor progression in which epithelial cells in breast tissue dedifferentiate to more malignant cells. Furthermore, increased expression of aromatase, the rate-limiting enzyme that catalyzes the conversion of androgens to estrogens, has been observed in the adipose tissue of mammary glands in obese women with breast cancer [18]. As both adipose tissue and breast cancer epithelium express aromatase, levels of circulating estradiol are especially elevated in overweight or obese women with breast cancer [18]. This has particular clinical significance for women with ER-positive disease, as increased aromatase expression has been demonstrated to contribute to poorer prognosis in obese breast cancer patients [20].

In addition to adiposity, dietary fat is postulated to contribute to carcinogenesis through the synthesis of certain eicosanoids or lipid compounds metabolized from fatty acids that support tumor growth [12]. In diets high in animal fat, the abundance of omega-6 fatty acids can be used in the production of eicosanoids that promote inflammation and tumor angiogenesis. Prostaglandin E2 (PGE2) is the most abundant pro-inflammatory eicosanoid identified in breast cancer and has been shown to stimulate tumor cell proliferation through aromatase upregulation [21]. As aromatase is encoded by the
examined the association between cruciferous vegetable intake and risk of recurrence among tamoxifen users \( n = 1765 \) and found that women who were in the highest reported vegetable intake tertile at baseline had overall lower hazard for breast cancer recurrence \( \text{HR} = 0.48; 95\% \text{ CI} 0.32–0.70; p = 0.005 \).

### Low-Fat, High Fruit, and Vegetable Diet and Risk of Breast Cancer Recurrence: Plausible Mechanisms

The postulated mechanisms underlying a high intake of fruits and vegetables in reducing the risk of recurrence are related to the role of plant-derived foods as a source of chemopreventive compounds and having the ability to lower circulating estrogen concentrations. The anticarcinogenic properties of such a dietary pattern have been attributed to high levels of phytonutrients, including carotenoids, polyphenols, and isothiocyanates [22]. Preclinical data investigating the cancer-preventative activity of phytonutrients support this hypothesis, as the carotenoid lycopene was demonstrated to inhibit IGF-1-induced [26] and estrogen-induced proliferation in breast cancer cells [27]. Yet, despite evidence for the inhibitory action of phytonutrients on breast cancer cell proliferation, and observational data supporting an inverse relationship between phytonutrient consumption and risk of recurrence [25], phytonutrient interventions demonstrating actual inhibition of estrogen- and IGF-1 dependent signaling in breast cancer patients have yet to be conducted.

The second mechanism by which diet composition may influence disease recurrence and survival is through an effect on reproductive hormones. A high-vegetable, high-fiber, low-fat diet intervention has been associated with a significant reduction in serum estradiol concentrations in women diagnosed with early-stage breast cancer, even without loss of body weight [28]. However, fiber intake was also found to be independently related to reductions in serum estradiol concentrations, suggesting that increased fiber, rather than decreased fat intake, may have been responsible for reductions in circulating estrogen in these breast cancer patients. The biological mechanism supporting the role of fiber in positive breast cancer outcomes is related to its ability to bind to estrogen, as fiber supplementation in female rats with mammary tumors resulted in increased fecal excretion and inhibition of intestinal reabsorption of estrogen [29]. Taken together, these results suggest a potentially beneficial influence of fiber on breast cancer recurrence due to reductions in circulating estrogen. However, as no direct evidence exists to support this conclusion, interpretation of the epidemiological data is limited.

### Soy and Vitamin D Intake and Risk of Breast Cancer Recurrence

At present, no RCTs have been conducted expressly incorporating soy or vitamin D as part of a diet intervention; therefore,
in the proceeding section, observational and preclinical data are discussed in relation to breast cancer survival.

Conflicting data exists between epidemiological and preclinical investigations on the role of soy intake in breast cancer recurrence. While the epidemiological data has found no association between soy intake and adverse breast cancer events [30–34], the in vitro and in vivo data have raised concerns on the safety of phytoestrogens in breast cancer survival. Soy foods, such as soy milk and tofu, are rich in isoflavones that are structurally similar to the primary endogenous estrogen 17β-estradiol [32]. A major isoflavone in soy products is genistein, which can compete for binding to the ER in breast tissue, although the binding affinity of isoflavones for the ER is a magnitude lower than that of 17β-estradiol [35]. As such, isoflavones have traditionally been regarded as ER modulators that can exhibit estrogen-like properties, potentially promoting mammary tumorigenesis [30]. However, the concerns surrounding the relationship between genistein and breast tumor proliferation have been questioned in a recent review, with evidence cited to support the anticarcinogenic effects of genistein while disputing its stimulatory effects [35]. For example, in a DMBA (7,12-dimethylbenz[a]anthracene) model of induced mammary carcinoma, female rats exposed to genistein during the early neonatal period had reduced incidence of mammary tumors compared to control rats [36], while in an orthotopic model of breast cancer, mice who received genistein supplementation exhibited a 10-fold lower metastatic burden compared to control mice [37]. Yet, the authors acknowledge preclinical data reinforcing the stimulatory effect of genistein on established ER-positive mammary tumors, albeit at a rate lower to estradiol. In contrast, the epidemiological data unequivocally refutes the dangers of isoflavones in breast recurrence, with data from 4 large clinical trials reporting no adverse relationship between soy intake and breast cancer prognosis [30–32, 34], and 1 observational trial in fact reporting a statistically significant reduced risk of recurrence with a post-diagnosis soy food consumption ≥10 mg isoflavones/day (HR = 0.75; 95% CI 0.61–0.92) [33]. Thus, despite the extensive research investigating the adverse effect of isoflavones on mammary tumorigenesis, it appears from observational data that soy-derived genistein does not negatively impact breast cancer recurrence, particularly in ER-negative disease. However, before clinical guidelines can be proposed, RCTs incorporating soy products in a dietary intervention are warranted to demonstrate clear evidence that soy intake is safe and possibly chemopreventive.

Similarly, investigations on the relationship between vitamin D intake and breast cancer recurrence have been limited to preclinical and observational data, with additional insight provided by correlative studies nested in RCTs comprised of women with early-stage breast cancer. Though evidence from in vitro, animal, and observational studies support the role of vitamin D in improving breast cancer outcomes, data from prospective [38] and observational studies nested randomized trials [39, 40•, 41] in women with breast cancer have not suggested prognostic associations [39, 40•, 41]. The physiological mechanism underpinning the inhibitory action of vitamin D on breast cancer centers on calcitriol, the hormonally active form of vitamin D. Calcitriol inhibits proliferation of human breast cancer cell lines and arrests tumor growth in xenograft models through several processes that ultimately suppress estrogen pathways in breast cancer cells (reviewed in Krishnan et al. [42]). Briefly, calcitriol reduces estrogen synthesis through direct repression of CYP19 and through decreases in PGE2. In addition to reducing estrogen synthesis, calcitriol downregulates ERα expression, suppressing the action of estrogen. The mechanistic evidence is in agreement with observational data supporting an adverse association between breast cancer recurrence and levels of serum 25-hydroxyvitamin D [25(OH)D], the precursor to calcitriol [43, 44]. In contrast, findings from observational studies contradict these results, as no associations between serum 25(OH)D levels and breast cancer outcomes have been observed in a secondary analysis of the WHEL data [38], or in adjuvant (MA.21 [40•], MA.14 [41]) or neo-adjuvant (I-SPY [39]) settings. Although the nesting of observational studies in randomized trials such as that in Clark et al. [39], Lohmann et al. [40•], and Pritchard et al. [41] has its limitations, the RCTs provide greater standardization of tumor, treatment, and outcome characterizations than the non-therapeutic observational studies. Clearly, therapeutic interventions involving vitamin D supplementation would be desirable in evaluating the effects of vitamin D on breast cancer outcomes, as neither observational nor post hoc correlative studies provide substantive evidence on which to base recommendations.

Summary and Current Dietary Recommendations

Though results from the large-scale WHEL and WINS randomized trials do not support an effect of low-fat/high fruit and vegetable diets on overall survival, evidence from WINS and a secondary analysis of the WHEL data have potentially demonstrated a benefit of a reduced-fat diet on risk of recurrence. As the positive findings from WINS and the secondary analyses of WHEL were associated with weight loss or hormonal status, the mechanism by which a reduced-fat diet may exert its beneficial effects may be mediated through metabolic hormones and factors associated with decreased adiposity. Furthermore, although data from randomized trials is lacking, soy intake does not appear to be adversely related to breast cancer outcomes nor are low vitamin D levels unequivocally associated with recurrence or increased mortality. Despite the limited evidence supporting diet interventions in preventing breast cancer recurrence, recent recommendations for cancer survivors from the American Cancer Society (ACS) [6] underscore the growing importance of a healthy diet across the
Physical Activity/Exercise and Risk of Breast Cancer Recurrence

For the purposes of this review, physical activity (PA) is defined as any movement requiring energy expenditure, while exercise is PA that is planned, structured, and directed to enhance physical fitness and health [4]. “PA” will be used when referencing epidemiologic studies and “exercise” when referring to RCTs.

An increased risk of breast cancer recurrence in breast cancer survivors (~34%) compared to physically active breast cancer survivors has been, in part, attributed to sedentary lifestyle behaviors [46]. Since exercise has been shown to elicit numerous health benefits including improved quality of life, increased physical functioning, reduced cancer-related fatigue as well as reductions in obesity-related comorbidities in cancer survivors [47–49], the plausible effects of exercise on breast cancer recurrence are important to consider. Although there have been efforts to ameliorate the side effects breast cancer-related treatments with increased aerobic and resistance exercise [50–52], the evidence is lacking to provide information on the effects of exercise on breast cancer recurrence. This section presents evidence from both epidemiological and clinical trials examining the effect of PA or exercise on breast cancer recurrence outcomes. In addition, possible mechanisms elucidating the relationship between PA/exercise and disease recurrence will be discussed.

PA and Risk of Breast Cancer Recurrence: Epidemiologic Evidence

Previously published review articles have summarized the effects of PA on breast cancer events and mortality [3, 5, 53], including the recent systemic review summarized here [54–]. This systemic review and meta-analysis included 22 prospective studies and, in brief, found an inverse relationship between PA and all-cause, breast cancer-related death and breast cancer events (i.e., recurrence). For example, compared to those who reported low/no lifetime recreational pre-diagnosis PA, women who reported high lifetime recreational pre-diagnosis PA levels had a significantly lower risk of all-cause (HR = 0.82, 95% CI 0.70–0.96, p < 0.05) and breast cancer-related death (HR = 0.73, 95% CI 0.54–0.98, p < 0.05). Significant risk reductions for all-cause and breast cancer-related death was observed for more recent (~12 years) pre-diagnosis recreational PA (HR = 0.73, 95% CI 0.65–0.82, p < 0.001; and HR = 0.84, 95% CI 0.73–0.97, p < 0.05, respectively), post-diagnosis PA (HR = 0.52, 95% CI 0.43–0.64, p < 0.01; and HR = 0.59, 95% CI 0.45–0.78, p < 0.05, respectively), and meeting recommended PA guidelines (i.e., ≥8 MET-h/week; MET or metabolic equivalent, is a concept used to express the energy cost of physical activities as a multiple of resting metabolic rate where 1 MET if the amount of oxygen consumed while sitting at rest) post-diagnosis (HR = 0.54, 95% CI 0.38–0.76, p < 0.01; and HR = 0.67, 95% CI 0.50–0.90, p < 0.01, respectively). Pre-diagnosis (lifetime and more recent combined) and post-diagnosis PA were associated with reduced risk of breast cancer events (breast cancer progression, new primaries and recurrence...
The effect of exercise on breast cancer recurrence is an area currently under much speculation yet evidence from RCTs is lacking. However, pertinent to this area is the Supervised Trial of Aerobic versus Resistance Training (START) multicenter Canadian RCT which recently reported an exploratory analysis of follow-up cancer outcomes in breast cancer survivors [56••]. The START trial randomized 242 breast cancer survivors to usual care, supervised aerobic, or resistance training while undergoing adjuvant chemotherapy. For this analysis, the 2 exercise groups were combined (n = 160) to examine the effect on disease-free survival (DFS). Eight-year DFS was lower for the exercise groups (82.7 %) compared with the usual care group (75.6 %; HR, 0.68; 95 % CI, 0.37–1.24; log-rank, P = 0.21). Subgroup analyses resulted in potentially stronger effects of exercise on DFS for women who were overweight/obese (HR, 0.59: 95 % CI, 0.27–1.27), had stage II/III cancer (HR, 0.61: 95 % CI, 0.31–1.20), estrogen
improve insulin or IGF-1 levels, even in the absence of fat loss. One possible explanation for the reductions in circulating concentrations of sex hormone binding globulin (SHBG), a protein that binds to estrogen to decrease its bioavailability [60]. To date, 4 RCTs utilizing exercise interventions with metabolic hormones as primary endpoints have been conducted in breast cancer survivors [61–64], yet only 3 have demonstrated that chronic exercise training can improve insulin or IGF-1 levels [61, 62], even in the absence of fat loss [63]. One possible explanation for the differences in efficacy between Schmitz et al. [64] and the 3 interventions can be attributed to exercise prescription, as the 3 interventions met the American College of Sports Medicine (ACSM)/ACS exercise recommendation for cancer survivors of at least 150 min/week of moderate intensity exercise or 75 min/week of vigorous intensity exercise [6]. In addition, the 3 interventions employed aerobic training (AT), with Ligibel et al. [63] utilizing a combined program of AT and resistance training (RT), while Schmitz et al. [64] employed only RT. Another explanation for differing results between the investigations is the enrollment of sedentary, obese breast cancer survivors in the studies of Irwin [62] and Ligibel [63] compared to the leaner and more active women in Schmitz’s study. Baseline concentrations of insulin were lower in Schmitz’s participants; hence, exercise interventions may have greater effect in less active breast cancer survivors with higher adiposity. Yet, Schmitz et al. also reported significant increases in skeletal muscle following RT, which conceivably could contribute to improvements in whole-body glucose tolerance and insulin resistance [59]. However, Schmitz et al. observed no changes in insulin resistance following RT, suggesting that future exercise interventions in breast cancer survivors should incorporate higher intensities, greater volume or employ AT in addition to RT to elicit optimal changes in cardio-metabolic variables.

While increased concentrations of insulin and IGF-1 may affect estrogen levels, as previously discussed in the diet section, bioavailable estrogen is also independently influenced by adiposity. Elevated levels of circulating estrogens have been attributed to excess adipose tissue and increased expression of aromatase, the enzyme that catalyzes estrogen synthesis, in the breast tissue of obese breast cancer survivors [18]. As estrogenic stimulation has been shown to promote tumorigenesis and breast cancer pathogenesis, higher adiposity has been suggested to contribute to poorer prognosis in obese breast cancer patients [20]. Exercise may favorably alter bioavailable estrogen through either mechanism, although separating the effects of fat loss from reductions in insulin/IGF-1 due to exercise has not yet been elucidated in breast cancer survivors. Rock et al. [60] demonstrated significant reductions in bioavailable estrogen in post-menopausal breast cancer survivors following a combined physical activity and diet intervention. As this finding was observed alongside significant weight loss of 5 %, increased SHBG, and decreased insulin and leptin concentrations, the authors hypothesized that the reductions in estrogen were likely mediated by fat loss.

Leptin alone has been associated with a more aggressive tumor type in post-menopausal breast cancer survivors with ER-positive disease [65]. As leptin is secreted from white adipose tissue, higher circulating levels have been observed in overweight/obese breast cancer survivors compared to lean patients [66••]. Leptin promotes the recruitment of macrophages, which in turn, release pro-inflammatory cytokines, contributing to a chronic state of systemic inflammation that...
has been purported to correlate with poorer prognosis in breast cancer survivors [67]. As such, an intervention that reduces adiposity would be expected to decrease leptin concentrations alone or in combination with reductions in macrophage-produced inflammatory cytokines. Evidence supporting the use of exercise training in lowering leptin concentrations in breast cancer survivors is emerging, with one RCT demonstrating significant improvements in leptin in overweight breast cancer survivors following a 3-month intervention of 150 min/week of exercise, although non-significant changes were observed in the inflammatory markers IL-6, tumor necrosis factor (TNF)-α, and IL-10 [67]. This finding suggests that leptin levels in breast cancer survivors are responsive to exercise, and if leptin is indeed related to recurrence, then exercise may be a useful therapeutic in improving breast cancer outcomes. Future investigations are needed to determine the role of exercise and its potential mechanisms in favorably altering adipokine concentrations in breast cancer survivors.

Summary and Current Exercise Recommendations

Epidemiological evidence supports the participation in PA before and after breast cancer diagnosis as a contributing factor in decreasing risk of breast cancer recurrence and mortality. Supportive data from RCTs to promote exercise as a means to reduce disease recurrence is lacking; however, promising data from the sole RCT reviewed here examining the effects of exercise on disease outcomes [56] suggests that there may be beneficial effects of exercise on breast cancer recurrence. Additional RCTs are necessary to guide specific exercise recommendations to target disease recurrence.

Current recommendations set forth by ACSM [68], ACS [69], and the US Department of Health and Human Services [70] (Table 1) encourage cancer survivors to follow exercise prescription for healthy age-matched adults (aged 18–64 years) which includes 150 min per week of moderate or 75 min per week of vigorous aerobic exercise. Muscle-strengthening activities or resistance exercise involving all major muscle groups should be performed 2 days per week; however, these exercises should be led by a trained exercise specialist to ensure the intensity is progressed appropriately. Use of compression garments during exercise is recommended per guidance from a healthcare professional.

Combined Diet and PA and Risk of Breast Cancer Recurrence

Due to the independent physiologic effects of diet and physical activity on adiposity, inflammation, and hormonal regulation, a more potent stimulus to target breast cancer recurrence may involve a combined diet and physical activity intervention. In this section, we will discuss the few clinical [71**, 72, 73] and epidemiologic [74] investigations assessing a combined diet and physical activity intervention on breast cancer recurrence or survival.

Combined Diet and PA and Risk of Breast Cancer Recurrence: Epidemiologic Evidence

Although the focus of this manuscript is on lifestyle intervention effects on breast cancer recurrence, it is important to recognize a hallmark epidemiologic study including combined diet and PA as it influences mortality due to the long-term observations afforded by this study. This includes the WHEL study [8] previously mentioned in the diet portion of this review that will be expanded upon here as it pertains to diet and PA [74].

The WHEL is a prospective cohort study including 1490 women treated for early-stage breast cancer between 1991 and 2000 who enrolled approximately 2 years post-diagnosis. Interactions between lifestyle factors and mortality were examined. Dietary patterns were assessed at baseline using 2 24-h dietary recalls on random days during a 3-week period using a telephone-based dietary assessment with associated analysis software. PA was assessed at baseline using a 9-item questionnaire on usual PA with queries on frequency, duration, and intensity used to determine metabolic equivalent (METs) values.

Importantly, reduced mortality was weakly associated with higher fruit and vegetable consumption (p = 0.02), increased PA (p = 0.02), and normal BMI (p = 0.06). Using a Cox multivariate model, the combination of consuming 5 or more daily servings of fruits and vegetables, and accumulating 540+ MET tasks-min/week (or walking 30 min 6 days/week) was associated with improved survival (HR = 0.56; 95% CI, 0.31 to 0.98, p = 0.04). Notably, the approximate 50% reduced risk was observed in both obese and non-obese women. Univariate analysis demonstrated that high fruit and vegetable intake and high PA levels were advantageous on survival for hormone receptor-positive cancers (ER-positive, PR-negative; p = 0.04; ER-positive, PR-positive; p = 0.01). The latter result suggests the mechanism of action may involve reproductive gonadal hormones as previously suggested for diet and PA lifestyle factors on prognosis.

Despite the observational nature of the WHEL study, it emphasizes the relationship between lifestyle factors and disease prognosis in a large cohort of women with early-stage breast cancer. These results have since been used to implement intervention trials as will be discussed in the subsequent section.

Combined Diet and PA and Risk of Breast Cancer Recurrence: Evidence from Clinical Trials

As obesity is a major risk factor breast cancer recurrence and morbidity in pre- and post-menopausal women [5, 75, 76], targeting reductions in body weight through combined diet and exercise interventions have been conducted. Three RCTs will be
discussed, including the Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) trial [71••], a smaller yet pertinent RCT from Scott and colleagues [72], and an ongoing RCT—the Diet and Androgens (DIANA)-5 study [73].

The ENERGY trial is the largest weight loss intervention trial among breast cancer survivors to date [71••]. This multicenter trial included 692 overweight/obese women who were approximately 2 years from primary treatment for early-stage breast cancer. Women were randomized to either a group-based behavioral intervention with telephone counseling and newsletters to support weight loss or a less intensive control intervention including weight management resources and materials. The goal of the intervention was a 7% weight loss in 2 years and included weekly 1-h group sessions for the first 4 months tapering to every other week for 2 months followed by monthly from month 6 onward. Dietary guidance promoted a reduction in energy intake of 500–1000 kcal/day and a PA goal of an average of 60 min/day at a moderate intensity. Body weight was measured at 6, 12, 18, and 24 months.

At 12 months, the intervention group experienced a mean weight loss of 6.0% of initial weight compared to 1.5% in the control group (p < .001). At 24 months, the group differences remained significant (p < .001) with mean weight loss of 3.7 and 1.3% for the intervention and control groups, respectively. This finding implies that a behavioral weight loss intervention can result in clinically meaningful weight loss in this population. Although the authors are unable to report the effect of the intervention on recurrence and survival at this point in time, they report that a 4–6% weight loss substantially reduces circulating levels of estrogens and cytokines, which are implicated mediators of breast cancer recurrence.

Scott et al. (2013) examined the effects of a diet and PA intervention on body weight in overweight breast cancer survivors in an effort to determine the relationship between body weight and biomarkers associated with disease recurrence and survival [72]. Ninety women treated for early-stage breast cancer in the previous 3–18 months were randomly assigned to a 6-month exercise and hypocaloric healthy eating program or control group. The physical activity portion included 3 weekly 30-min aerobic exercise (65–85% age-predicted heart rate maximum) sessions followed by 10–15 min of muscle-strengthening exercises using resistance bands, hand weights and stability balls under supervision. The dietary intervention included one-on-one individualized dietary advice and written information pertaining to portion sizes and a healthy eating plan. The goal of the dietary intervention was a reduction in total daily caloric intake by 600 kcal from their calculated energy requirements. Collectively, the authors purported that this intervention would result in an estimated weight loss of up to 0.5 kg/week.

The intervention resulted in moderate weight loss (median difference from baseline of −1.09 kg; p = 0.07) in the intervention group and a significant reduction in waist circumference (p < 0.001). Biomarkers associated with long-term prognostic outcomes of breast cancer including leptin (p = 0.005), total cholesterol (p = 0.046), and HDL (p = 0.015) were significantly altered. Positive changes in leptin and total cholesterol were significantly associated with reductions in body weight and waist circumference (p < 0.01; R values not reported by authors). The authors concluded that a 6-month exercise and hypocaloric eating program positively impacted health outcomes (i.e., weight, waist circumference, leptin) that influence long-term prognosis in overweight breast cancer survivors.

These 2 RCTs provide strong implications for the impact of combined diet and exercise on breast cancer recurrence with the ENERGY trial relying on home-based interventions and Scott’s trial including supervised, clinic setting interventions. Both trials did not directly assess survival rates yet rather measured outcomes strongly linked to prognosis such as central adiposity, sex hormones, lipid profiles, and pro-inflammatory biomarkers, which have been discussed previously in this manuscript. Each trial provides evidence of strong effects of a combined intervention on weight loss with their respective study designs, thus implicating the need for future RCTs with long-term follow-up assessments to link these changes with disease recurrence.

A notable ongoing RCT is the Diet and Androgens (DIANA)-5 study, which is a multicenter RCT examining the effectiveness of a Mediterranean diet and PA intervention on breast cancer events between 2008 and 2010, followed through 2015 [73]. The intervention consists of a counseling program with cooking classes, exercise sessions, and reinforcing meetings and print materials. The PA goals are to participate in a moderate intensity PA program of 210 min/week (2–5 METs) over at least 3 days/week and to decrease sedentary behavior by 30 min/day on at least 5 days/week. During the first 12 months, 1 group PA session/month is offered to increase PA adoption. The diet program focuses on reducing glycemic and insulinenic responses through (1) moderate caloric restriction through increased consumption of highly satiating foods (refined cereals, legumes, and vegetables), (2) reduced consumption of high glycemic index food, (3) reduced consumption of saturated fat, and (4) reduced protein intake, particularly animal protein (except fish). Outcomes include recurrence, death from breast cancer, and death from any cause. The investigators seek to establish a comprehensive lifestyle modification to increase breast cancer event-free survival. The results of such a trial may be the first to establish breast cancer outcomes affected by a diet and PA intervention.

Summary

Despite the lack of concrete epidemiologic and clinical evidence supporting the effects of combined diet and PA lifestyle modifications on breast cancer recurrence, the aforementioned studies emphasize the benefits of such behaviors on health...
outcomes biologically linked to recurrence. Further, these studies shed light on the need to study diet and exercise interventions moving forward to specifically define parameters to guide the adoption of lifestyle behaviors targeting disease-free survival. In the interim, dietary and exercise guidelines outlined in Table 1 provide a comprehensive foundation that breast cancer survivors can rely upon to adopt a healthier lifestyle during survivorship.

Conclusions

In evaluating evidence from RCTs involving diet, exercise, or combined diet and exercise interventions, the most consistent finding was that reductions in adiposity accompanied the most beneficial changes in breast cancer outcomes, including survival, risk of recurrence, or biomarkers associated with prognosis. These data suggest that body composition is a crucial, modifiable risk factor for breast cancer prognosis, and interventions targeting fat loss and skeletal muscle gain may yield improvements that translate to clinically meaningful outcomes. While data from currently conducted RCTs is still emerging, a combined intervention of diet and exercise appears to hold the most promise in modifying the incidence of additional breast cancer events or mortality and is also reinforced by epidemiological evidence. Yet, the lack of conclusive evidence supporting whether exercise- or diet-induced changes can occur independent of changes in fat mass necessitates future work examining the complex interaction between adiposity, energy balance, and breast cancer recurrence. Regardless, the data evaluated in this review support the use of both dietary modification and increased exercise as a means of improving overall health and reducing risk of recurrence and mortality in breast cancer survivors.

Compliance with Ethical Standards

Conflict of Interest  Christina M. Dieli-Conwright, Kyuwan Lee, and Jacqueline L. Kiwata declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent  This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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