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Lifestyle Interventions for Breast Cancer Prevention

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Abstract

One-in-eight women in the United States will develop breast cancer in her lifetime. Despite the established efficacy of selective estrogen receptor modulators and aromatase inhibitors in reducing the risk of developing hormone receptor positive breast cancer, use of these therapies in clinical practice is often limited by concerns over toxicities that may negatively influence quality of life. There is emerging interest in the oncology community to understand how modifiable risk factors related to energy balance—such as obesity, physical inactivity, and poor dietary patterns—may relate to breast cancer risk. Over the past three decades, observational studies have reported that obesity, physical inactivity, sedentary behavior, and dietary patterns are associated with increased breast cancer risk. However, uncertainty exists about whether the observed associations are attributable to confounding from other factors. Randomized controlled trials are necessary to provide unbiased efficacy estimates of lifestyle changes on breast cancer risk. However, such trials would typically require a large sample size, long-term follow up, and substantial financial investment. One approach to manage these barriers is to leverage recent advances in precision prevention to select high-risk study participants to reduce sample size or shorten length of follow up. This approach may accelerate the translation of epidemiologic discoveries into proven population-based breast cancer prevention interventions.

Keywords

breast neoplasms; obesity; adiposity; physical activity; diet; randomized clinical trial; epidemiology

INTRODUCTION

One-in-eight women (12.4%) in the United States will develop breast cancer in her lifetime, representing an increase compared to one-in-eleven (9.1%) in the 1970s [1]. In 2018, an estimated 266,120 incident cases of invasive breast cancer will be diagnosed, and 40,920 women will die from breast cancer [1], making breast cancer the most common female malignancy, accounting for 29% of all invasive cancers diagnosed in women, and the second most common cause of cancer-related mortality in women.

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Breast cancer prevention strategies to date have largely focused on the use of medications that block the activity of estradiol (selective estrogen receptor modulators [SERMS]) and therapies that prevent peripheral conversation of androgen precursors to estradiol (aromatase inhibitors [AIs]). Both categories of agents have been shown to significantly reduce the risk of hormone receptor positive breast cancer by up to 75% in randomized clinical trials. However, the uptake of these agents in clinical practice has been limited due to concerns regarding toxicities and inaccurate perceptions of breast cancer risk. Nearly 10-million women in the United States are eligible to use these agents for primary breast cancer prevention [2], yet less than 15% elect to use this type of therapy [3, 4]. In addition, there are no proven prevention strategies for hormone receptor negative breast cancers. Although these cancers account for only 15–20% of breast cancers diagnosed, they contribute disproportionally to breast cancer deaths [1].

Given the lack of uptake of chemoprevention for breast cancer—and the lack of proven strategies for the prevention of hormonally insensitive breast cancer—there is emerging interest in the oncology community to understand how modifiable risk factors related to energy balance, such as obesity, physical inactivity, and poor dietary patterns, may relate to breast cancer risk. This interest is synergized by the curiosity of patients to understand how modifiable health behaviors may influence their individual risk of developing cancer.

The prevalence of modifiable risk factors related to energy balance has reached epidemic proportions in the United States. More than one-third of adults (37.7%) have obesity [5]. Fewer than one-in-ten adults (9.7%) engages in ≥ 150 minutes/week of objectively-measured moderate- or vigorous-intensity physical activity [6]. Nearly one-in-two adults (45.6%) self-report consuming a poor diet, (e.g., minimal fruit, vegetable, whole grain, and fish consumption) [7]. All of these modifiable risk factors related to energy balance have been associated with breast cancer risk [8], and the elimination of these risk factors may prevent up to 30% of incident breast cancers [9, 10].

This report provides a review on the study of modifiable risk factors related to energy balance for breast cancer prevention, including an overview of the observational and interventional evidence linking lifestyle factors to breast cancer and an exploration of the biological mechanisms through which lifestyle factors could impact breast cancer risk. The report concludes with a look to the future of lifestyle intervention, with the goal of identifying more efficient ways to establish the ability of weight loss, increased physical activity and improved dietary quality to prevent breast cancer.

ENERGY BALANCE AND BREAST CANCER RISK: OBSERVATIONAL STUDIES

Over the past three decades, observational studies have reported that lifestyle factors related to energy balance are associated with breast cancer risk. The three broad domains of lifestyle factors include obesity, physical activity/sedentary behavior, and dietary patterns. Herein, we briefly describe the evidence supporting the association between these selected lifestyle factors and breast cancer risk.

Obesity

In 2003, a landmark study of 495,477 U.S. women demonstrated that obesity was associated with a 62% higher risk of developing and dying from cancer [11]. Compared to women with a body mass index of 18.5–24.9 kg/m^2, those with a body mass index ≥40 kg/m^2 were two-fold more likely to develop and die from breast cancer. Following this publication, dozens of additional studies have evaluated the relationship between body mass index and breast cancer risk. In 2016, the International Agency for Research on Cancer (IARC) convened a working group of 21 independent international experts to assess the effects of obesity on cancer risk. This working group systematically reviewed more than 1000 studies that investigated the relationship between obesity and cancer risk and determined there was *sufficient* evidence to conclude that obesity is associated with an increased risk of developing multiple types of cancer, including postmenopausal breast cancer [12]. For each 5 kg/m^2 increase in body mass index, the risk of developing postmenopausal breast cancer increases by 10%. Based on this data, the IARC working group concluded that the absence of excess body fatness lowers the risk of many cancers, including postmenopausal breast cancer. This conclusion was corroborated by the World Cancer Research Fund (WCRF) continuous update project [13].

Physical Activity

In 2007, WCRF International convened a panel to review the evidence examining the association between physical activity and cancer risk [14]. The panel reviewed more than 250 studies and determined there was *sufficient* evidence to conclude that participation in physical activity is associated with a decreased risk of developing multiple types of cancer, including postmenopausal breast cancer [14]. This conclusion was confirmed in a large pooled analysis using 12 studies of 1.44-million adults [15]. This pooled analysis concluded that participation in physical activity was associated with a lower risk of developing multiple different types of cancer, including breast cancer. Higher levels of self-reported physical activity were associated with a 10% relative risk reduction in breast cancer risk, compared to a lower self-reported physical activity. It is hypothesized that one of the mechanisms by which physical activity may lower cancer risk is through the regulation of adiposity [16]. However, adjustment for body mass index only attenuated the inverse association between physical activity and breast cancer risk by 3.3%, and this association remained statistically significant. This observation suggests that physical activity may lower breast cancer risk through mechanisms other than the control of adiposity (as described later in this review).

Sedentary Behavior

Independent of physical activity, engaging in sedentary behavior is a risk factor for cancer risk and other poor health outcomes. Sedentary activities are characterized by sitting or lying, and often include screen-based activities such as TV viewing, and smartphone and computer use. In a meta-analysis of observational studies, higher levels of sedentary behavior were associated with a 17% higher risk of developing breast cancer [17]. In another meta-analysis, sedentary behavior was associated with an increased risk of all-cause mortality (22%), cardiovascular disease mortality (15%), cancer mortality (14%), and incidence of type 2 diabetes (91%) [18].

Dietary Patterns

Certain self-reported dietary patterns may be associated with breast cancer risk. Dietary patterns are commonly classified as being Western (high intake of refined grains, fats, red and processed meats, and sugar sweetened beverages) or prudent (high intake of whole grains, fruits, vegetables, chicken, and fish). In a meta-analysis of 18 observational studies, women who adhered to a prudent dietary pattern were 11% less likely to develop breast cancer during the follow up period than women who did not adhere to such a dietary pattern [19]. The WCRF concluded there is limited but suggestive evidence that non-starchy vegetables, dairy products, foods containing carotenoids, and diets that are high in calcium are associated with a lower risk of developing breast cancer [13]. Conversely, consumption of alcohol is associated with an increased risk of developing breast cancer; for each 10 grams per day of alcohol consumption, risk of pre and postmenopausal breast cancer increases by 5% and 9%, respectively [13].

Energy Balance in Women with Hereditary Risk Factors

Although more limited, emerging evidence suggests that energy balance related lifestyle factors are associated with breast cancer risk in women with hereditary risk factors for developing breast cancer. For example, among 1,008 women with inherited mutations in *BRCA1* and *BRCA2*, physical activity as an adolescent and healthy body weight at menarche and age 21 were associated with delayed onset of breast cancer [20]. Several other studies have demonstrated that obesity, weight gain, and total energy intake are associated with a higher risk of developing breast cancer [21, 22], whereas weight loss is associated with a lower risk of developing breast cancer among *BRCA1/2* mutation carriers [23]. These data are consistent with the hypothesis that lifestyle behaviors which shift energetic homeostasis may reduce the risk of developing breast cancer, even among women at high risk of developing breast cancer due to hereditary risk factors [24].

LIFESTYLE AND BREAST CANCER RISK: MECHANSISMS AND RANDOMIZED CLINICAL TRIALS

Mechanisms that Link Energy Balance with Breast Cancer Risk

The specific biologic mechanisms that link obesity, physical activity, sedentary behavior, and dietary patterns to breast cancer risk have not been fully elucidated. It is hypothesized that these energy balance related lifestyle factors may alter breast cancer risk through multiple mechanisms, including low grade systemic inflammation, immune function, and unfavorable concentrations of insulin and other metabolic hormones such as leptin and sex steroids, that may promote a host tumor microenvironment that encourages malignant cell growth and progression [25, 12, 16]. For example, elevated concentrations of C-reactive protein (a biomarker of chronic systemic inflammation) are independently associated with 23–45% higher risk of developing breast cancer [26]. Obesity is associated with local inflammation within the breast tissue, characterized by necrotic adipocytes surrounded by macrophages forming crown-like structures [27]. These crown-like structures are associated with elevated concentrations of pro-inflammatory mediators and aromatase expression [28]. Type 2

Diabetes Mellitus, characterized by a state of insulin resistance and resultant hyperinsulinemia, is associated with a 27% higher risk of developing breast cancer [29].

Impact of Lifestyle Interventions on Biologic Measures Linked to Breast Cancer Risk

Multiple phase II randomized controlled trials have examined how lifestyle interventions that alter energy balance through weight loss, increased physical activity, reduced sedentary time, and dietary modification may influence these hypothesized physiologic mediators. Perhaps the one randomized clinical trial that has provided the most abundant insight on the physiologic mechanisms that may mediate the relationship between lifestyle and cancer risk is the Nutrition and Exercise in Women (NEW) study. NEW was a 12-month phase II randomized controlled trial using a four-arm design to compare the effects of three lifestyle interventions, including aerobic exercise, dietary weight loss, or both aerobic exercise and dietary weight loss combined versus control (no lifestyle change) on an array of biologic endpoints in 439 postmenopausal women aged 50–75, with a body mass index ≥25 kg/m^2, who at baseline engaged in <100 minutes/week of exercise. This trial demonstrated that compared to usual care, the combination of aerobic exercise and dietary weight loss favorably changed body mass (−10.8% vs −0.8%; P<0.001) [30], insulin resistance (−26% vs −2%; P<0.001) [31], inflammation (C-reactive protein: −36.7% vs +8.4; P<0.001) [32], serum estrone (−11.1% vs +8.1%; P<0.001) and testosterone (−5.9% vs 1.8%; P=0.02) [33], and the expression of several genes related to steroid hormone metabolism and growth factor signaling [34]. Compared to aerobic exercise alone, dietary weight loss alone resulted in larger improvements in many of these physiologic outcomes in this sample of overweight and obese women. This phase II randomized trial, and others [16], provide evidence that lifestyle modifications induces a variety of favorable physiologic changes that may alter breast cancer risk. These trials are useful to refine the design of lifestyle interventions that can be tested in a phase III setting with a clinical endpoint.

Randomized Lifestyle Breast Cancer Prevention Trials

Two large randomized clinical trials have evaluated the effects of dietary modification on incident breast cancer (Table 1). The Women's Health Initiative Randomized Controlled Dietary Modification Trial, tested the hypothesis that a low-fat dietary pattern reduces the risk of developing invasive breast cancer in a sample of 48,835 postmenopausal women. The intervention was designed to promote dietary change towards the goals of reducing total fat intake to 20% of total energy and increasing consumption of fruits and vegetables to ≥5 servings daily and grains to ≥6 servings daily. At year 6, compared to control, the intervention group reduced percentage of energy from fat by 8.1%, increased fruit and vegetable consumption by 1.1 servings per day and grain consumption by 0.4 servings per day (all P<0.001). After a median of 8.1 years of follow up, the dietary intervention did not result in a statistically significant reduction in breast cancer risk [Hazard Ratio: 0.91; 95% Confidence Interval: 0.83–1.01] [35]. In addition, this intervention did not significantly reduce the risk of major adverse cardiovascular events [Hazard Ratio: 0.93; 95% Confidence Interval: 0.83–1.05] [36], or the risk of developing type 2 diabetes mellitus [Hazard Ratio: 0.96; 95% Confidence Interval: 0.90–1.03] [37]. The dietary modification group lost a modest amount of weight compared to the control group [1.9 kg difference at 1 year and 0.4 kg between group difference at 7.5 years] [38].

In contrast, the PREDIMED (Prevención con Dieta Mediterránea) trial, tested the hypothesis that an unrestricted-calorie high-vegetable-fat Mediterranean diet supplemented with extra virgin olive oil or mixed nuts would reduce the risk of invasive breast cancer (pre-specified secondary outcome) in a sample of 4,282 women with cardiovascular disease risk factors. After a mean follow up of 4.8 years, the Mediterranean diet supplemented with olive oil was associated with a significant reduction in breast cancer risk [Hazard Ratio: 0.32; 95% Confidence Interval: 0.13–0.79] [39]. This provides a hypothesis generating observation, as breast cancer was a secondary endpoint, and during the follow up period only 35 confirmed incident cases of breast cancer were identified. This intervention significantly reduced the risk of experiencing the primary study endpoint of a major adverse cardiovascular event [Hazard Ratio: 0.70; 95% CI: 0.54–0.96] [40], and developing type 2 diabetes mellitus [Hazard Ratio: 0.49; 95% Confidence interval: 0.25–0.97] [41]. Compared to the control group, the Mediterranean diet with extra virgin olive oil induced small, but statistically significant, reductions in body mass [−0.43 kg at 5 years] and waist circumference [−0.55 cm at 5 years] [42].

DESIGNING THE NEXT GENERATION OF LIFESTYLE CANCER PREVENTION STUDIES

Most evidence that supports an association between energy balance related lifestyle factors and breast cancer risk is derived from observational study designs. A major limitation to observational research is that such associations may be confounded if people who have certain energy balance related lifestyle risk factors also have other disease risk factors or disease screening patterns that cannot be completely accounted for in the statistical analysis [43]. Consequently, uncertainty exists about whether the observed associations are attributable to confounding from other factors [44]. Obtaining an unbiased estimate of efficacy about a lifestyle intervention on breast cancer risk can only be achieved within the context of a randomized controlled clinical trial. Such definitive studies will provide persuasive evidence to shape clinical practice paradigms in cancer prevention.

Despite randomized controlled clinical trials being the gold standard to demonstrate intervention efficacy, trials in the primary prevention of breast cancer typically require a large sample size (in the thousands or tens of thousands), long-term follow up (a minimum of half a decade), and substantial financial investment (in the order of tens of millions). Investigators have estimated the sample size necessary to demonstrate the benefit of an energy balance related lifestyle intervention on invasive breast cancer. For example, a trial that enrolls postmenopausal women age 45–75 years, to have 80% statistical power detect a 20% relative risk reduction (0.3% absolute risk reduction from 98.4% *vs* 98.7%), would require 29,450 women accrued over an interval of 7.3 years, with a minimum of 5 years of follow up [44]. Although possible, it is unlikely that a trial of this size and scope will be conducted in the United States. Consequently, there is a need to identify other means to conduct definitive trials to generate evidence that will shift cancer prevention policy and practice.

One approach is to leverage recent advances in “precision prevention” [45] to recruit a population that has a higher baseline risk of developing breast cancer during the follow up period. Such an approach would reduce the required sample size or allow the follow up duration to be shortened. Herein, we provide an example of how emerging approaches in precision prevention can be utilized to more efficiently design randomized clinical trials for breast cancer prevention. The approach provided is considered an enrichment strategy [46].

One approach is to utilize breast cancer risk prediction models that integrate information beyond family history and reproductive factors that can better discriminate women at higher risk of developing breast cancer. For example, utilizing data from the Breast and Prostate Cancer Consortium (BPC3), investigators developed a risk prediction model that integrates a polygenic risk score with family history, anthropometric factors, menstrual and reproductive factors, and lifestyle factors [47]. This new risk prediction model can identify 5% of the population with a lifetime risk of developing breast cancer above 22.0%. The spread in the distribution of risk by modifiable risk factors, such as body mass index, was larger for strata of the population that were at higher risk of developing breast cancer. For example, the population attributable risk (PAR) of high body mass index in the overall population was 12.1%; among women in the lowest decile of risk, the PAR of body mass index was 0.57%, whereas in the highest decile of risk, the PAR was 2.1%. It was noted that nearly one-fifth of all preventable cases of breast cancer occurred the top decile of predicted cancer risk, whereas only 4% of preventable cases arise from the population in the lowest decile of predicted risk.

The observation that patients at high risk of developing cancer can derive substantial benefit from energy balance related lifestyle intervention is like what has been reported in the field of cardiology. For example, among patients at high genetic risk of developing cardiovascular disease, participation in a healthy lifestyle (no smoking, no obesity, regular physical activity, and a healthy diet) was associated with a 46% lower relative risk of developing coronary events [48]. Relevant to the design of clinical trials of breast cancer prevention, new risk prediction models can provide greater precision and discrimination for identifying women at high risk of developing breast cancer, who can then be targeted for participation. This approach may: 1) reduce the necessary sample size by increasing the baseline rate of developing a breast cancer over a fixed duration of follow up; or 2) shorten the duration of follow up by reducing the median time to developing a breast cancer given a fixed sample size.

CONCLUSIONS

One-in-eight women in the United States will develop breast cancer in her lifetime. Pharmacotherapies, including SERMs and AIs, significantly reduce the risk of developing invasive breast cancer. However, uptake of these chemoprevention strategies is hampered by concern regarding toxicity and lack of interest in taking a medication by an otherwise healthy person. There is growing evidence from observational studies that lifestyle factors related to energy balance, such as obesity, physical activity, sedentary behavior, and dietary patterns, may be associated with breast cancer risk. However, few of these observational associations have been confirmed by randomized clinical trials. Such randomized trials often

require very large sample sizes, long term follow up, and significant investment of financial resources, rendering them impractical in many countries. Leveraging the emergence of precision prevention methods as an enrichment strategy would allow prevention trials to be conducted more efficiently with smaller sample sizes or potentially shorter follow up duration. Definitive evidence from phase III trials are necessary to provide persuasive evidence to shape cancer prevention policy and practice. The efficient design and conduct of such definitive trials will accelerate the translation of epidemiologic discoveries into proven population-based prevention interventions.

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Table 1

Key Studies of Lifestyle Modification on Invasive Breast Cancer Risk

Trial	Intervention	Population	Sample Size	Primary End Point	Results	Subgroups
WHI Dietary Modification Trial[35]	Lifestyle intervention: Reduction of intake of total fat to 20% of energy and increase consumption of fruits and vegetables to ≥5 servings daily and grins to ≥6 servings daily or usual diet comparison group	Postmenopausal women, aged 50–79 years, without a prior breast cancer	48,835	IBC	After median follow up of 8.1 years, non-significant 9% relative reduction in risk of IBC, HR: 0.91; 95% CI: 0.83–1.01	22% reduction among women consuming ≥36.8% of energy from fat, HR: 0.78; 95% CI: 0.64–0.95 11% reduction among ER+ tumors, HR: 0.89; 95% CI: 080–1.00 24% reduction among PR− tumors, HR: 0.76; 95% CI: 0.63–0.92
PREDIMED[39]	Lifestyle intervention: Mediterranean diet supplemented with extra virgin olive oil Lifestyle Intervention: Mediterranean diet supplemented with mixed nuts Control diet (advice to reduce dietary fat)	Women aged 60–80 years at higher risk of developing cardiovascular disease	4,282	Major cardiovascular events Pre-specified secondary endpoint: IBC	After median follow up of 4.8 years, 68% relative reduction in risk of IBC with Mediterranean diet supplemented with extra virgin olive oil, HR: 0.32; 95% CI: 0.13–0.79)	E28% reduction for each additional 5% of calories from extra virgin olive oil, HR: 0.72; 95% CI: 0.57–0.90

Abbreviations: CI, Confidence Interval; ER, Estrogen Receptor; HR, Hazard Ratio; IBC, Invasive Breast Cancer; PR, Progesterone Receptor