Modifiable Lifestyle Factors: Opportunities for (Hereditary) Breast Cancer Prevention – a Narrative Review

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Keywords

BRCA1 / BRCA2 mutations · Breast cancer · Epidemiology · Health behavior · Hereditary breast cancer · Lifestyle · Nutrition · Obesity · Physical activity · Prevention

Summary

Increasing rates of obesity, lack of physical activity, sedentary behavior, and frequent alcohol consumption are major lifestyle-related risk factors for breast cancer. In fact, it has been estimated that about one-third of breast cancer cases are attributable to factors women can change. Most research has focused on examining the impact of one single exposure on breast cancer risk while adjusting for other risk modifiers. Capitalizing on big data, major efforts have been made to evaluate the combined impact of well-established lifestyle factors on overall breast cancer risk. At the individual level, data indicate that even simple behavior modifications could have a considerable impact on breast cancer prevention. Moreover, there is emerging new evidence that adopting a healthy lifestyle may be particularly relevant for women with hereditary susceptibility to breast cancer. On the absolute risk scale, studies suggest that the presence of certain risk factors, such as excessive body weight, had a substantially higher impact on breast cancer risk if women had a hereditary predisposition to cancer. The existing body of knowledge gives the medical professionals guidance as to which factors to focus on when counseling patients. However, well-designed randomized controlled trials utilizing objective methods are crucial to providing concrete recommendations.

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Introduction

Four out of ten cancer cases among US women are believed to be preventable by healthier lifestyle choices [1]. In particular, excessive body weight, physical inactivity, frequent alcohol consumption, and the increased availability of calorie-dense foods are adding to the growing breast cancer burden. Furthermore, these unhealthy lifestyle choices threaten to offset the steady decline in cancer mortality [2]. Yet, the American Society of Clinical Oncology identified serious gaps in public knowledge about lifestyle factors contributing to cancer risk: Despite obesity being a leading preventable cause of cancer, only 31% of the people surveyed recognized the link [3]. Major public health efforts are necessary to improve public awareness and to incorporate lifestyle recommendations into clinical practice which can be applied both at the individual and the collective level. Here, we review the emerging evidence on modifiable lifestyle factors across the lifespan that offer an opportunity for breast cancer prevention by means of healthier living – even in women with genetic susceptibility to breast cancer.

Studies considered for this review were obtained from PubMed searches based on the search terms breast cancer, hereditary breast cancer, *BRCA*, risk factor, lifestyle, weight, obesity, physical activity, exercise, sedentariness, diet, and smoking. We critically reviewed references of all relevant publications (including review articles) to identify additional articles. Only studies published after 2002 that evaluated breast cancer risk were included. Studies examining the impact of lifestyle factors on clinical outcomes among breast cancer survivors were excluded.

Excessive Body Weight, Distribution of Fat Mass, Insulin Signaling, and Breast Cancer Risk

A large body of research points to the fact that obesity increases a person's risk for at least 13 different types of cancer [4, 5], including postmenopausal breast cancer. The association between body weight and breast cancer risk varies by menopausal status: Evidence suggests that a high body mass index (BMI) may be associated with a decrease in premenopausal breast cancer risk, but is strongly associated with an increased risk of developing postmenopausal breast cancer [6]. A meta-analysis of cohort studies showed an 18% decreased risk of premenopausal breast cancer per 5 kg/m² increase in BMI during young adulthood [7]. In the Nurses' Health Study II, women indicating a BMI of ≥ 27.5 kg/m² at age 18 years had a 39% decrease in premenopausal breast cancer risk compared to their lean counterparts (BMI of 20.0–22.4 kg/m²) [8]. The reduction in premenopausal breast cancer risk with increasing BMI during the teen years has been attributed to irregular menstrual cycles and ovulatory infertility. Yet, after adjusting for these factors in the Nurses' Health Study II, they showed only little impact on the association [8]. Research suggests that body fatness at young ages may be associated with slower adolescent growth and lower levels of both progesterone and insulin-like growth factor 1 (IGF-1) [7, 9]. Still, the underlying biological mechanisms are not well-delineated and warrant further evaluation. Examining the role of obesity in premenopausal breast cancer in terms of specific tumor subtypes, Pierobon and Frankenfeld [10] observed a positive association between obesity and triple-negative breast cancer among premenopausal women, reporting an increase in risk of 43% (95% confidence interval (CI) 1.23–1.65).

Notably, adipose tissue is a major source of estrogen synthesis in postmenopausal women, an established risk factor in breast carcinogenesis, and evidence supports a clear association between body fatness and a substantially increased risk of postmenopausal breast cancer [11]. In a meta-analysis of prospective studies examining the association between BMI and postmenopausal breast cancer risk, Renehan et al. [12] found a 12% increase in risk per 5 kg/m² increase in BMI. Carpenter et al. [13] provided evidence that the positive association between BMI and postmenopausal breast cancer risk may be modified by family history of breast cancer: Postmenopausal women who had at least 1 first-degree relative with breast cancer and who had a current BMI of ≥ 27.1 kg/m² were at a 2.9 times greater breast cancer risk than women with a positive family history whose current BMI was < 21.7 kg/m² (95% CI 1.86–4.54).

Several studies examined the association between weight change throughout the women's lifespan, i.e., mostly weight gained from early adulthood to present, and subsequent breast cancer risk [11]. A key limitation of this measure is that it may miss any weight loss at varying time points in a woman's lifespan. Eliassen et al. [14] showed that a weight gain of at least 25 kg since age 18 years elevated postmenopausal breast cancer risk by 45% (95% CI 1.3–1.7, p -trend < 0.001) compared to women whose weight remained stable (weight fluctuations of ≤ 2 kg). A weight gain of at least 10 kg

following menopause conferred an 18% increased risk of breast cancer compared to a stable weight at the same period of time (95% CI 1.0–1.4, p -trend = 0.002) [14]. Based on data from the Women's Health Initiative observational study, Chlebowski et al. [15] demonstrated that a modest weight loss after menopause, i.e., a relative weight loss of at least 5% of one's body weight, could lower breast cancer risk by 12% relative to stable weight (95% CI 0.78–0.98).

In addition to a higher risk of developing breast cancer, overweight women tend to present with larger tumors at the time of diagnosis when compared with their normal-weight counterparts [16].

Case-control studies suggest that a woman's body fat distribution may influence the hormone receptor status of the breast cancer she is susceptible to [17]. Both general and central obesity have been associated with greater breast cancer risk [11]. Obese women with larger amounts of subcutaneous fat, as measured by BMI, may have a significantly higher risk of developing hormone receptor-positive breast cancer. In contrast, larger amounts of visceral fat, indicated by a high waist-to-hip ratio, may be associated with a greater risk of developing hormone receptor-negative breast cancer, independent of BMI [17].

As scientists continue to explore the relationship between obesity and cancer, there is rapidly increasing interest in the insulin signaling pathway [18]. Based on data from the Women's Health Initiative Study, Gunter et al. [19] conducted a case-control analysis to prospectively examine the incidence of postmenopausal breast cancer among nondiabetic women. Their findings suggest that insulin levels were positively associated with breast cancer risk (hazard ratio (HR) 1.46; 95% CI 1.00–2.13; p -trend = 0.02), confirming that hyperinsulinemia is an independent risk factor for postmenopausal breast cancer. While experimental evidence supports a synergistic interaction between estrogen receptor activation and increased IGF-1 signaling with regard to breast carcinogenesis, the data from the prospective European Prospective Investigation into Cancer and Nutrition (EPIC) cohort indicate that higher circulating IGF-1 levels may increase the risk of hormone receptor-positive breast cancer diagnosed after age 50 years (odds ratio (OR) 1.38, 95% CI 1.01–1.89; p -trend = 0.01) [20].

Physical Activity and Breast Cancer Risk

Numerous scientific studies have demonstrated a protective role of physical activity in breast cancer etiology, and anthropometric factors do not attenuate this association [11]. Collectively, the evidence supports an inverse association between physical activity and breast cancer, with a risk reduction of 20–30% when comparing the most physically active to the least active women [21, 22] and depending on the study design, population studied, and level of physical activity. The relationship exists for both pre- and postmenopausal women, with greater risk reductions observed among postmenopausal women [7, 21]. The magnitude of risk reduction appears to be stronger for strenuous than for moderate levels of exercise [21, 23].

Both retrospective and prospective studies confirmed a dose-response relationship between increasing levels of physical activity and breast cancer risk, and the association was true for all pathological subtypes of cancer [11, 24]. In the Nurses' Health Study II, adolescent physical activity from ages 14–17 years was inversely associated with premenopausal breast cancer risk, with a risk reduction of 19% (95% CI 0.69–0.95) [25].

Even though research provides consistent findings linking physical activity to breast cancer, a big limitation of these studies is the reliance on women's self-reports instead of objectively measured data. To date, only one research group used accelerometer data to evaluate the association between physical activity level and breast cancer incidence [6]. Among 2,160 Polish women, Dallal et al. [26] reported a 61% decrease in risk for women in the highest quartile of moderate-to-vigorous accelerometer-based measures of physical activity compared to women in the lowest quartile (95% CI 0.27–0.56; p -trend < 0.0001).

Sedentariness and Breast Cancer Risk

Long amounts of time spent sitting have been shown to influence breast cancer risk, and the positive association seems to be independent of physical activity. Based on accelerometer data and after adjustment for physical activity, Dallal et al. [26] found an 81% increased risk of breast cancer in women with the longest sedentary time compared to women with the shortest duration of sitting (95% CI 1.26–2.60; p -trend = 0.001). With regard to occupational sedentariness, Johnsson et al. [27] observed a 20% increased risk of breast cancer diagnosed before age 55 years (95% CI 1.05–1.37) compared to women with less sedentary occupations. The results were replicated in a study of African-Americans evaluating the association between total time spent sitting and subsequent breast cancer risk [28].

Diet and Breast Cancer Risk

In separate studies, alcohol consumption emerged as the strongest and most consistent dietary factor linked with breast cancer. In 2017, the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) published a dose-response meta-analysis for premenopausal breast cancer which revealed a 5% increased risk per 10 g of ethanol consumed per day (95% CI 1.02–1.08) [7]. For postmenopausal breast cancer, the researchers observed a 9% increased risk per 10 g of ethanol consumed per day (95% CI 1.07–1.12) [7]. Findings indicate that frequent alcohol consumption may put a woman with at least 1 breast cancer-affected first-degree relative at greater risk for breast cancer than women with no family history [29].

Case-control studies suggest that balanced diets, consisting of substantial amounts of wholegrain, fiber, fruits, and vegetables, are associated with reduced breast cancer risk, especially when adopted early in life, i.e., during childhood [6]. Based on the Nurses' Health

Study II, Harris et al. [30] reported that an adolescent and early adulthood dietary pattern characterized by sugar-sweetened soft drinks, refined grains, red and processed meat, and margarine, and low intake of leafy vegetables and cruciferous vegetables was associated with an increased incidence of premenopausal breast cancer (HR 1.35; 95% CI 1.06–1.73; p -trend = 0.002 for adolescent diet, and HR 1.41, 95% CI 1.11–1.78; p -trend = 0.006 for early adulthood diet) [30]. In 2017, the WCRF/AICR indicated that only limited evidence exists for a decrease in breast cancer risk associated with the consumption of foods containing carotenoids or the consumption of non-starchy vegetables, respectively [7]. In fact, randomized controlled trials for studying diet-cancer relationships have failed to demonstrate a significant impact of diet on breast cancer risk. Only limited and non-significant trends exist for an association between a low-fat dietary pattern and reduced breast cancer risk [7, 11]. The EPIC study investigated the association between the adherence to the Mediterranean diet and risk of breast cancer among 335,062 European women, with an average follow-up of 11 years. The data indicate that adherence to the Mediterranean diet excluding alcohol was associated with a decrease in risk for postmenopausal breast cancer (HR 0.93; 95% CI 0.87–0.99; p -trend = 0.037), particularly in the case of hormone receptor-negative tumors (HR 0.80; 95% CI 0.65–0.99; p -trend = 0.043). The PREDIMED trial was the first randomized controlled trial to support these findings, providing additional evidence for a protective effect of a Mediterranean diet, supplemented by extra virgin olive oil, in breast cancer, with a decrease in risk of 68% (95% CI 0.13–0.79) [31]. Well-designed prospective studies focusing on diet patterns rather than dietary components are warranted to address the critical gap in the current literature regarding the role of diet in breast cancer risk.

Smoking and Breast Cancer Risk

The relationship between smoking and breast cancer has been studied extensively; however, findings have been inconclusive [11]. Emerging evidence derived from better-designed epidemiologic studies suggests a positive association between breast cancer and tobacco consumption in populations with high smoking prevalence, higher pack-years, and long durations of smoking [11, 32–34]. In the largest cohort examined, Dossus et al. [33] provide evidence that both active and passive smoking contribute to a substantially increased risk of breast cancer, particularly for increasing pack-years of active smoking between menarche and first full-term pregnancy (HR 1.73, 95% CI 1.29–2.32 for every increase of 20 pack-years).

Joint Impact of Lifestyle Factors on Breast Cancer Risk

Since cancer predisposition is multifactorial in origin, caused by a complex interplay between genetic factors and a multitude of

non-genetic exposures such as environmental influences, reproductive and lifestyle factors – many of them occurring concomitantly, modifiable risk assessment cannot simply be reduced to a single hypothetical factor. Failure to include relevant exposures most possibly results in decreased power and biased risk estimates, whereas considering a large amount of potential influences may lead to challenges in both statistical implementation and interpretation, particularly in correlated factors. Further, both preventive and harmful lifestyle behaviors tend to appear in clusters. Recently, major efforts have been made to evaluate the combined impact of selected lifestyle factors on breast cancer risk. Based on data from the EPIC study, McKenzie et al. [35] evaluated a healthy lifestyle index score (HLIS) to investigate the joint effect of 5 modifiable lifestyle factors on postmenopausal breast cancer risk. The HLIS is composed of diet, physical activity, smoking, alcohol consumption, and anthropometric factors, with higher values indicating healthier behaviors. With each point added to a person's HLIS, postmenopausal breast cancer risk decreased by 3%, suggesting that an overall healthy lifestyle may substantially lower the risk of developing postmenopausal breast cancer. Ellingjord-Dale et al. [36] replicated these findings in a Norwegian cohort. Risky lifestyle behaviors were defined as follows: ever-smoking, weekly consumption of >2 glasses of alcoholic beverage, <3 h leisure time physical activity weekly, ever-use of menopausal hormone therapy, and BMI > 25 kg/m². There was a linear dose-response relationship between the number of risky lifestyle behaviors and hormone receptor-positive breast cancer: Women who had 5 risky lifestyle behaviors were at a 2.38 times greater risk of luminal A-like breast cancer compared to women with no risky lifestyle behaviors (95% CI 1.58–3.59; p-trend < 0.0001). Taken together, these findings show preliminary evidence that an overall healthy lifestyle may contribute to a sizeable decrease in breast cancer risk.

Impact of Modifiable Risk Factors on *BRCA*-Associated Breast Cancer

Women who inherit a deleterious *BRCA1* or *BRCA2* mutation face a high lifetime risk of developing breast cancer, between 69 and 72% [37] compared to 12% in the general population [38]. Among *BRCA* mutation carriers, primary prevention of breast cancer is limited to prophylactic bilateral mastectomy; however, mutation carriers frequently inquire about less invasive prevention options [39]. Both the incomplete penetrance and the regional differences in penetrance of an inherited *BRCA1* or *BRCA2* mutation suggest that environmental exposures may influence risk [40]. While various reproductive and hormonal factors have shown to impact *BRCA*-associated cancer risk [41], suggestive evidence exists that lifestyle factors, including body weight, adolescent physical activity, calorie restriction, and non-smoking, may contribute to a decrease in the number of *BRCA*-associated breast cancer cases [42, 43].

In an early study, King et al. [44] reported that the risk for early-onset breast cancer was lower if gene mutation carriers were born

before 1940, had given birth, had a healthy weight at menarche and age 21, and were physically active during adolescence. Kotsopoulos et al. [45] showed that a weight loss of at least 10 pounds between ages 18 and 30 was associated with a 53% decreased risk of *BRCA*-associated breast cancer between ages 30 and 49 (95% CI 0.28–0.79). Pijpe et al. [46] demonstrated a significant 42% reduction in risk (95% CI 0.35–0.94; p-trend = 0.05) with increasing levels of physical activity prior to, but not after, age 30. In addition to mechanistic data linking physical activity to reductions in endogenous sex hormone levels, lower IGF-1 levels, and an improved immune function [22, 47], gene-environment interactions are of increasing research interest with regard to *BRCA*-related tumors. Using an in vivo model, Wang et al. [48] demonstrated that prepubertal physical activity was associated with a significant increase in *BRCA1*, *p53*, estrogen receptor (*ER*)- α , and *ER*- β mRNA expression in mammary glands of adult rats versus control (unexercised) rats (p < 0.03). We recently reported that, even in a small study cohort of 68 *BRCA* mutation carriers, study participants indicating a higher level of physical activity during adolescence had a significantly lower cancer prevalence (p = 0.019) [49]. Additionally, we observed a significantly higher cancer prevalence in smokers compared to non-smokers (p < 0.001) [49]. Pettapiece-Phillips et al. [50] showed that uninterrupted sedentary behavior was associated with decreased *BRCA1* mRNA expression (p = 0.02). Whether this finding translates into a potentially harmful effect with regard to *BRCA*-associated cancer risk is under active study. Nkondjock et al. [51] reported a positive association between total energy intake and *BRCA*-associated breast cancer risk when comparing the highest tertile of calorie intake with the lowest tertile (OR 2.76, 95% CI 1.10–7.02; p-trend = 0.026). In another analysis, Nkondjock and Ghadirian [52] demonstrated that a balanced diet of high quality was associated with a 65–82% decreased risk of *BRCA*-related breast cancer (OR 0.35, 95% CI 0.12–1.02; p-trend = 0.034 for Diet Quality Index-Revised (DQI-R) and OR 0.18, 95% CI 0.05–0.68; p-trend = 0.006 for Canadian Healthy Eating Index (CHEI)). However, analyses were all limited by a retrospective study design with small sample sizes, providing significant potential for biases.

Trygvadottir et al. [53] investigated changes in penetrance over time with regard to the cumulative breast cancer incidence before age 70 years in Icelandic women. The investigators found a 4-fold increase in the cumulative incidence of breast cancer between 1920 and 2000 among *BRCA2* mutation carriers (from 18.6 to 71.9%) and women in the general population (from 1.8 to 7.5%). Indeed, on the absolute risk scale, the adoption of a healthy lifestyle will affect breast cancer risk to a considerably greater extent among women with a hereditary susceptibility to breast cancer compared to women without a family history of cancer. Quante et al. [54] evaluated the performance of the IBIS Breast Cancer Risk Evaluation Tool, with and without accounting for BMI, for predicting breast cancer occurrence in postmenopausal women. The authors found a significant absolute BMI-induced difference in IBIS-assigned 10-year risk, comparing women with a BMI of 27 kg/m² to women with a BMI of 21 kg/m² with regards to hereditary predisposition to cancer: The absolute BMI-induced difference in the

model-assigned 10-year risk ranged from 0.3% for women with neither affected first-degree relatives nor a *BRCA1* mutation to 4.5% for mutation carriers with 3 breast cancer-affected relatives. Additionally, at the individual level, Quante et al. [54] demonstrated that overweight women who had originally been classified as 'high risk' patients for developing breast cancer could be reclassified as 'low risk' only by reducing their BMI.

Among *BRCA* mutation carriers, two independent studies demonstrated that the receipt of a positive *BRCA1/2* genetic test result contributed to significant lifestyle changes [55, 56]. We recently reported that women with hereditary *BRCA* mutations tend to adopt healthier lifestyles compared to women from the general population [49]. However, radical changes in health behavior could potentially result in the uptake of harmful behaviors. For instance, given the widespread use of folic acid supplementation, research efforts have been made to elucidate the relationship between folate status and breast cancer risk. Even though the role of folate in the development of *BRCA*-related breast cancer is not clear, Kim et al. [57] indicated that elevated plasma folate concentrations might be associated with an increased risk for breast cancer among *BRCA* mutation carriers.

A prospective evaluation of multiple lifestyle behaviors, collected at various time points, with the utilization of objective methods to capture body size, physical activity, and dietary habits, is crucial to provide evidence-based, safe, and effective strategies for this high-risk group. Moreover, providing measurable data is necessary to facilitate the counselees' understanding of both non-modifiable and modifiable risk information [58].

Aiming to elucidate the impact of non-genetic modifiers on *BRCA*-associated breast cancer risk, the LIBRE study is the first prospective randomized lifestyle intervention trial worldwide in-

volving cancer-affected and -unaffected *BRCA* mutation carriers [59, 60]. The purpose of the randomized, 2-armed (1:1), multicenter, interdisciplinary, prospective, and open study is to demonstrate that a structured intervention program, consisting of endurance training paired with the Mediterranean diet, will improve BMI, physical fitness, and adherence to the Mediterranean diet pattern. The long-term goals of the trial are to demonstrate a decrease in breast cancer risk, an inhibited progression of disease, and a reduced cancer mortality rate in *BRCA* mutation carriers following a healthy lifestyle. Ultimately, by utilizing a variety of objective methods and by analyzing the joint effects of modifiable lifestyle factors, the LIBRE trial aims to provide data on lifestyle options of preventive value that could be translated into the practice of genetic counseling.

Conclusion

Building upon the growing evidence linking lifestyle factors to (*BRCA*-associated) breast cancer, we suggest that action should be taken to incorporate timely lifestyle recommendations into the daily practice of clinicians and genetic counselors. To begin with, maintaining a healthy weight, limiting alcohol consumption, smoking cessation, and being physically active on a regular basis is a message medical practitioners and patients can act upon until more precise recommendations can be made.

Disclosure Statement

The authors declare that they have no conflict of interest.

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