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Impact of Lifestyle Factors on Prognosis Among Breast Cancer Survivors in the USA

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Abstract and Introduction

Abstract

Advances in diagnostic screening and adjuvant therapy have dramatically increased the number of breast cancer survivors in the USA, who may face changes in physical and mental health, social support, quality of life and economics. Women living with breast cancer are increasingly interested in lifestyle modification to decrease the risk of recurrence and mortality while increasing physical and emotional wellbeing. Although organizations such as the American Cancer Society support a healthy diet, frequent physical activity and stress reduction for decreasing breast cancer risk, studies examining the effects of lifestyle on clinical outcomes including survival and prognosis have been inconclusive. With the number of breast cancer survivors predicted to increase to 3.4 million by 2015, it is important to develop effective treatment paradigms that overcome barriers to behavioral modification to improve clinical outcomes and survivorship in breast cancer patients.

Introduction

Breast cancer is the most frequently occurring cancer in women and is second only to lung cancer in lethality. Over the last 50 years, lifetime risk of breast cancer has increased such that today one in eight women are expected to develop breast cancer. Projections indicated that more than 230,000 new breast cancers would be diagnosed and approximately 40,000 women would die from breast cancer in the USA in 2011.[1] Mortality rates increased from 1970 to 1990, but in recent years death rates have decreased by 28%.[2] This notable decline in mortality, likely attributable to improvements in early detection and adjuvant therapy,[3] has produced more than 2.5 million breast cancer survivors in the USA today[201] but this number is expected to increase to 3.4 million by 2015.[4]

The term 'breast cancer survivor' applies to individuals from the time of diagnosis through the remainder of their life, and includes patients recently diagnosed with breast cancer, undergoing active treatment or post-treatment follow-up, as well as those living with terminal disease. These survivors face numerous issues, including detrimental changes in physical activity, social support, psychological health and personal finance, which can impact long-term survival and quality of life (QoL).[5] Survivors may suffer from anxiety, depression, fear of recurrence, impaired body image and increased risk of comorbid conditions.[6–8] Although factors that influence survival are often not the same as those affecting QoL, and interventions designed to address one outcome may be ineffective in modifying the other, it is imperative to understand how lifestyle modification can improve relapse-free survival and/or QoL in breast cancer survivors.

Standard treatment for breast cancer in the USA includes surgery with or without radiation, hormone therapy and chemotherapy. Although state-of-the-art medical care has increased the number of survivors, these treatments often result in significant negative sequelae and many women suffer recurrence or breast cancer mortality. Studies of behavioral modification in breast cancer survivors are providing new information about how lifestyle factors such as diet, physical activity and stress affect survivorship, as well as knowledge to develop new and more effective intervention programs for survivors. Our main thesis in this review is that lifestyle changes in breast cancer survivors may complement traditional medical treatments and improve clinical outcomes such as recurrence and survival. Beginning with an overview of the relationship between obesity and breast cancer, we then examine data from large prospective cohort studies and randomized controlled trials investigating the role of diet on breast cancer prognosis. Although information is currently limited on other dietary factors that may have lesser impact on long-term survival, we consider the possible effects of alcohol, functional foods and nutraceuticals. We then discuss how physical activity may improve prognosis and highlight recent sentinel studies that have fundamentally changed the management of lymphedema. As complementary and alternative medicine (CAM) approaches, which are currently outside the standard of care, are gaining in popularity among breast cancer survivors, we examine whether therapeutic approaches to stress reduction actually improve patient survival or affect QoL. We conclude with discussions of lifestyle modification in patients with metastasis, who have different health concerns than women with early-stage disease, limitations to current study

designs and barriers to widespread implementation of lifestyle modification strategies.

Methods

Relevant English literature was identified by searching the PubMed database using the search terms "breast cancer survivor" along with "obesity", "diet", "physical activity", "stress", "group support", "yoga", "lymphedema" or "strength training".[202] We focused on large epidemiological studies and meta-analyses to ensure the most thorough and up-to-date synthesis of available data. Owing to the extensive and diverse nature of scientific research in this area, we conducted a broad overview of lifestyle factors rather than an exhaustive treatise of each lifestyle modality.

Obesity & Breast Cancer Prognosis

Nearly 36% of adult women in the USA are now obese (BMI >30 kg/m^2),[9] and are at increased risk for a number of health conditions such as diabetes, cardiovascular disease and various forms of cancer.[10] Obesity is associated with metastasis recurrence, a shorter disease-free interval and overall survival, and a greater likelihood of treatment failure in breast cancer patients,[11,12] which may be influenced by hormone receptor status and disease stage at diagnosis. Similarly, weight gain after diagnosis is common among women with breast cancer, and is associated with increased mortality and disease recurrence.[13] Each 5-kg gain in weight is associated with a 13% increase in breast cancer mortality.[14] Factors associated with postdiagnosis weight gain include changes in metabolism and physical activity, menopausal and lymph node status, and the duration, intensity and composition of treatment.[15–17] As 41% of adults in the USA are predicted to be obese by 2015,[18] improved understanding of the relationships between obesity, lifestyle factors and prognosis is essential to developing effective strategies to improve breast cancer survival.

Diet & Breast Cancer Prognosis

Dietary Fat, Fiber, Fruit & Vegetable Intake

The Nurses' Health Study (NHS) was established in 1976 to follow 121,700 female nurses over time through periodic health assessment questionnaires. Food frequency data from 1982 NHS participants with invasive breast cancer collected over 10 years showed no association between dietary fat intake and mortality ().[19] The NHS investigators classified dietary patterns as prudent (high in fruits, vegetables, legumes, whole-grains and seafood) or Western (characterized by high amounts of refined grains, processed red meat, eggs and high-fat dairy products).[20] Among 2619 women with dietary data and a diagnosis of invasive breast cancer, those consuming a Western diet before and after diagnosis had a higher risk of all-cause mortality; however, diet did not impact breast cancer prognosis.[21] Additional research from the NHS showed no relationship between diet quality indices and breast cancer mortality.[22]

Table 1. Large-scale studies evaluating the effects of diet on breast cancer mortality and recurrence.

Study	Type	Participants	Dietary factor(s)	Results	Ref.
NHS	PC	1982	Fat intake	No association	[19]
▫	▫	2619	Prudent versus Western diet	No association	[21]
▫	▫	2729	Four dietary quality indices	No association	[22]
LACE	PC	2321	>100 foods, beverages, nutritional supplements and medicinal herbs	No association	[23]
▫	▫	1901	Prudent versus Western diet	No association	[24]
HEAL	PC	670	Quality versus poor diet	Reduced risk of breast cancer mortality with quality diet	[25]
▫	▫	746	Quality versus poor diet	Lower CRP levels with quality diet	[26]
▫	▫	688	Fiber, carbohydrates, glycemic index and glycemic load	Nonsignificant relationship between dietary fiber and breast cancer	[27]

				recurrence and mortality	
WINS	RCT	975 cases; 1462 controls	Low-fat diet versus minimal nutritional counseling	Cases had higher relapse-free survival	[28]
WHEL	RCT	1537 cases; 1551 controls	High-fruit/vegetable versus 5-A-Day for Better Health Program diet	No association	[29]

CRP: C-reactive protein; NHS: Nurses' Health Study; PC: Prospective cohort; RCT: Randomized controlled trial.

A second large, prospective cohort study, the LACE study, enrolled 2321 women from a California-based health-maintenance organization and the Utah cancer registry who were diagnosed with breast cancer between 1997 and 2000. Dietary intake of more than 100 foods, beverages, nutritional supplements and medicinal herbs was assessed by food frequency questionnaires. Preliminary data suggested that dietary patterns of women with breast cancer were similar to those in women free from breast cancer in the general population.[23] Similar to the NHS study, a Western diet was associated with an increased risk of all-cause mortality, but was not associated with breast cancer mortality.[24]

In the HEAL study, a significant number of African American and Hispanic participants were recruited from California (USA), Washington (USA) and New Mexico (USA). Women (n = 670) with early-stage breast cancer who consumed a better-quality diet (low in calories, added sugar, alcohol and saturated fat) had a 60% lower risk of all-cause mortality and an 88% lower risk of breast cancer-related mortality.[25] A quality diet was also associated with decreased levels of circulating inflammatory markers.[26] A recent report presented suggestive evidence that high dietary fiber consumption may be associated with reduced breast cancer events and total mortality, but results were not statistically significant.[27]

In contrast to the observational studies described above, the WINS is a randomized trial measuring the effects of a low-fat diet on relapse-free survival. Women in the intervention group (n = 975) undergoing standard treatment for stage I or II breast cancer followed a low-fat dietary intervention, while controls (n = 1462) received minimal nutrition counseling. The intervention group showed a significant decrease in fat intake and maintained lower fat consumption for more than 5 years, while patients in the control group showed no significant change in fat intake. After 60 months of follow-up, relapse-free survival was 24% higher in the intervention group overall; however, subgroup analysis detected more pronounced effects in women with hormone receptor-negative carcinomas, suggesting a differential influence of diet on breast cancer recurrence based on hormone receptor status.[28]

In the WHEL study, women with stage I–IIIA breast cancer were randomized to an intervention arm (n = 1537) or control arm (n = 1551). The intervention group consumed a high fruit and vegetable diet, with only 15–20% of calories from fat, while controls were advised to follow the 5-A-Day for Better Health Program diet recommended by the National Cancer Institute. Nutritional intake for both groups was similar at baseline, but after 4 years the intervention group increased vegetable consumption by 65%, fruit consumption by 25%, fiber consumption by 30% and decreased calories from fat by 13% compared with the control group. Despite improvements in nutrition, breast cancer event-free survival and mortality did not differ significantly between the intervention and control groups.[29]

Ethnic and geographic differences among patients may affect the relationship between diet and breast cancer prognosis. Recent studies indicate that breast cancer survivors from racially and ethnically diverse populations differ in levels of physical activity, long-term adherence to dietary interventions and rates of obesity,[30,31] which may predispose certain groups to recurrence or poor prognosis. The HEAL study was one of only a few large studies to detect an association between diet quality and breast cancer mortality, which may reflect an ethnically diverse patient population recruited from different geographic locations.

Alcohol

In a large meta-analysis that included 58,515 women with invasive breast cancer and 95,067 controls from 53 studies, the relative risk of breast cancer increased by approximately 7% (95% CI: 5.5–8.7%, $p < 0.00001$) for each additional 10 g (unit or drink) of alcohol consumed on a daily basis.[32] However, relationships between alcohol consumption and breast cancer survival have not been well defined. One study of 1268 women ≤45 years of age with invasive breast cancer assessed the effect of prediagnostic alcohol consumption on mortality and determined that women who consumed alcohol during the 5-year

period prior to diagnosis had a 30% decreased risk (hazard ratio: 0.7; 95% CI: 0.5–0.9) of breast-cancer-related mortality compared with nondrinkers.[33] Similarly, the population-based SEARCH study of 4560 breast cancer patients detected a 2% reduction in mortality risk for every unit of alcohol consumed per week.[34] In contrast, the LACE study detected a 1.3-fold increase in breast cancer recurrence and a 1.5-fold increase in mortality among overweight and obese women who had three to four alcoholic drinks per week.[35] Other studies have shown no relationship between alcohol consumption and survival.[36,37] Given the limitations of currently available data, a personal decision to consume alcohol should balance the protective effects of alcohol for cardiovascular health against the potential for increased breast cancer risk.[38]

Vitamins

Nearly 50% of adults in the USA use vitamin supplements, even though research has provided no convincing evidence of true beneficial effects.[39] At present, the US Preventive Services Task Force and the National Institutes of Health Office of Dietary Supplements and Office of Medical Applications do not recommend use of multivitamins for the prevention of chronic disease.[40,41] Furthermore, two large studies examining the impact of multivitamins on breast cancer risk, the Women's Health Study (WHS) and Women's Health Initiative (WHI), found that multivitamin use did not decrease the risk of developing breast cancer or influence overall mortality.[42,43]

Although multivitamin supplements do not appear to impact breast cancer risk, specific vitamins may have beneficial effects on prognosis in breast cancer survivors. One study showed that premenopausal survivors diagnosed with node-positive breast cancer and low levels of retinol-binding protein, the carrier for vitamin A in plasma, had early disease recurrence.[44] In a separate study of postmenopausal women, low vitamin A levels were associated with poor outcomes such as distant metastasis and increased mortality.[45] In a study of 516 postmenopausal women with breast cancer from Orange County (CA, USA), women with the highest folate intake had lower mortality risk and vitamin C was significantly associated with decreased all-cause mortality. Nutrients derived from diet, rather than supplements, were believed to provide the survival advantage.[46] In the LIBCSP (n = 1508 women), vitamins B1 and B3 were associated with a 46 and a 39% lower risk, respectively, of all-cause mortality. Vitamin B1 intake was associated with decreased breast cancer mortality.[47] In the Shanghai Breast Cancer Survivor Study of 4877 women with breast cancer, vitamin C intake was associated with a 44% decrease in all-cause mortality and a 38% decrease in breast cancer recurrence.[48] Finally, although one group found significantly higher levels of circulating 25-hydroxyvitamin D in women with early-stage disease compared with patients with locally advanced or metastatic breast cancer,[49] other studies suggest that vitamin D consumption following treatment may have no survival advantage.[50]

The American Cancer Society (ACS) currently recommends that survivors consider using multivitamins with 100% of the daily recommended values to ensure proper nutrition. Nearly 75% of breast cancer patients report taking multivitamins to bolster their immune system and make treatment more effective. The data presented here demonstrate that levels of specific vitamins, rather than multivitamin consumption, may affect breast cancer outcome, but it is unclear whether these vitamins should be derived through diet or supplements to be most beneficial.

Green Tea

Consumption of green tea has long been customary in Asia, but the purported health-promoting benefits of green tea have been recognized only recently in the USA. Green tea contains a number of active ingredients including polyphenols, which may confer antimutagenic, antidiabetic, antibacterial, anti-inflammatory or hypocholesterolemic advantages.[51] In studies evaluating the effects of green tea consumption in 427 Japanese breast cancer survivors with stage I or II disease, recurrence was 16.7% in women who consumed five or more cups of green tea per day compared with 24.3% in those consuming less than five cups per day. This protective effect was not observed in patients with stage III breast cancer.[52] Likewise, in a second study of 1160 Japanese women, consuming three or more cups of green tea each day was protective against recurrence in women with stage I disease but showed no effect in more advanced cases.[53] A meta-analysis of these datasets showed that increased green tea consumption (more than three cups per day) was inversely associated with breast cancer recurrence.[54]

One possible explanation for the limited protective effects of green tea on recurrence in patients with advanced breast cancer involves the inhibitory action of polyphenols on angiogenesis and invasion. Inhibiting angiogenesis and invasive potential may be more important in early-stage tumors, which must develop a network of blood vessels and have not yet formed successful metastases, than in late-stage tumors that already have an extensive blood vessel network and invasive characteristics.[55]

Little information exists on the relationship between green tea consumption and survival in US breast cancer patients. Thus far,

studies of green tea and breast cancer have been performed mainly in Japanese populations where green tea is consumed routinely from an early age. It remains unclear whether health benefits observed in Japanese women will occur in women from other countries where lifetime consumption is much less.

Soy

A variety of health benefits have been attributed to consumption of soy-based foods, primarily due to soybean isoflavones such as genistein and diadzein. The chemical structure of isoflavones may enable these compounds to interact with human estrogen receptors, causing effects in the body similar to those induced by estrogen. Experimental studies in both cell lines and animal models suggest that genistein has the potential to stimulate cell proliferation, negatively influence prognosis and impair the effectiveness of tamoxifen therapy in estrogen receptor-positive breast carcinomas.[56,57]

Given the results of the experimental studies outlined above, which suggest that soy constituents can be estrogenic and potentially risk enhancing, an important question remains: do the estrogenic effects of soy influence prognosis and survival in humans? In population-based studies in the USA, women from the LIBCSP diagnosed with a first primary invasive breast carcinoma (n = 1210) showed reduced hazard ratios for all-cause mortality in the highest quintile of dietary intake compared with the lowest quintile for flavones, isoflavones and anthocyanidins. A decrease in breast cancer mortality was detected only in postmenopausal patients.[58] Other studies of diverse populations also observed significant inverse associations between soy consumption and breast cancer recurrence in postmenopausal women.[59,60] A recent meta-analysis observed that soy isoflavone consumption was inversely associated with breast cancer incidence and recurrence, but protective effects were only apparent in Asian populations, not in Western populations.[61]

Currently available data suggest that dietary intake of soy-based foods may confer a protective advantage for postmenopausal women with breast cancer; however, these benefits may be largely restricted to Asian populations where long-term soy intake is much higher. Additional health benefits, such as lower cholesterol and improved bone health, have been attributed to consumption of soy-based foods, but intake of isoflavones at high concentrations typically found in dietary supplements may be detrimental. Until the issue is fully resolved, physicians should allow patients receiving hormonal therapy or patients who have estrogen receptor-positive breast cancer to consume moderate amounts of soy as part of a balanced diet, but may recommend avoiding soy supplements.

Physical Activity & Breast Cancer Prognosis

Large cohort studies consistently demonstrate the importance of physical activity on breast cancer mortality and survival (). Data from the NHS from 2987 women with stage I–III breast cancer showed that any amount of exercise above three metabolic equivalent task (MET) hours per week (the equivalent of walking at a moderate pace of 2–3 miles per hour for 1 h) had a beneficial effect on survival. In patients with the highest activity, breast cancer recurrence and mortality were 26–40% lower than in women with the lowest activity.[62] In the LACE study, higher self-reported physical activity was significantly associated with lower all-cause mortality in 1970 breast cancer survivors.[63] The CWLS, which examined 4482 women diagnosed with breast cancer between 1988 and 2001, suggested that women who engaged in >2.8 MET hours per week had a 35–49% lower risk of breast cancer-related mortality compared with those who were physically inactive, even after adjusting for confounding factors such as disease stage, treatment modality, BMI and age at diagnosis. Moderate activity appeared to provide the greatest benefit, with vigorous activity providing no additional survival advantage.[64] Likewise, women in the HEAL study who were physically active in the year immediately prior to diagnosis or 2 years postdiagnosis showed significantly lower breast cancer mortality than women who were inactive. Women who decreased their activity after diagnosis had a fourfold increase in mortality, while those who increased their activity had a 45% lower risk of death.[65] Among 4643 postmenopausal women in the WHI study, those who engaged in ≥9 MET hours/week of recreational physical activity before diagnosis had lower all-cause mortality compared to women who were inactive. Importantly, women with ≥9 MET hours/week after diagnosis had lower all-cause and breast cancer mortality, even if they were inactive before diagnosis.[66] Results from the WHEL trial showed that among 2361 breast cancer survivors, women who were most active following treatment had a 53% lower mortality risk compared with the least active women.[67]

Table 2. Large-scale studies evaluating the effects of physical activity on breast cancer mortality and recurrence.

Study	Type	Participants	Physical activity†	Results	Ref.

NHS	PC	2987	MET hours per week	Lower breast cancer mortality with ≥9 MET hours/week	[62]
LACE	PC	1970	General activity during 6 months prior to enrolment	Lower total mortality associated with higher activity	[63]
CWLS	PC	4482	Postdiagnosis recreational activity	Lower breast cancer mortality with greater levels of activity	[64]
HEAL	PC	933	Physical activity in year prediagnosis and 2 years postdiagnosis	45% lower total mortality with increased activity postdiagnosis; fourfold increase in total mortality with decreased activity	[65]
WHI	PC	4643	Physical activity prediagnosis and 3–6 years postdiagnosis	Lower total mortality with ≥9 MET hours/week prediagnosis; lower breast cancer and total mortality with ≥9 MET hours/week postdiagnosis	[66]
WHEL	PC	2361	Physical activity at baseline and 1 year later	35% lower total mortality with ≥10 MET hours of moderate activity/week	[67]

†All physical activities were self-reported.
MET: Metabolic equivalent task; NHS: Nurses' Health Study; PC: Prospective cohort; WHI: Women's Health Inititative.

Recent meta-analyses, which include many of the prospective cohort studies mentioned above, support the positive role of physical activity on breast cancer outcomes. One meta-analysis evaluating 12,108 patients with breast cancer from six studies found that physical activity before diagnosis was associated with an 18% reduction in all-cause mortality, while physical activity after diagnosis reduced breast cancer mortality by 34%, all-cause mortality by 41% and disease recurrence by 24%.[68] In a second analysis of 13,302 women from four studies, the After Breast Cancer Pooling Project observed that engaging in ≥10 MET hours/week of moderate physical activity was associated with a 27% reduction in all-cause mortality and a 25% reduction in breast cancer-related mortality compared with women engaging in <10 MET hours/week.[69]

Research has shown that in addition to the beneficial effects on mortality and survival, physical activity can lower the risk of developing breast cancer.[70–72] Nevertheless, fewer than 50% of patients undergoing treatment, especially chemotherapy, engage in regular physical activity. As demonstrated in the HEAL study, physical activity decreased by approximately 2 h per week after diagnosis compared with activity levels 1 year before diagnosis.[73] Similarly, Belgian women (n = 267) with invasive breast cancer showed a significant decrease in activity during the first month postdiagnosis, and did not resume normal activity levels during the first year.[74]

Most research to date strongly supports the link between physical activity and improved breast cancer prognosis, as well as a reduction in comorbid conditions such as cardiovascular disease and diabetes. Despite these findings, several issues, such as the optimal form of physical activity, the frequency and duration of activity and an individualized versus a standardized activity regimen, remain unresolved. Most studies indicate that moderate-intensity aerobic exercise provides the most benefit in terms of prognosis, prompting organizations such as the US Department of Health and Human Services, ACS and American College of Sports Medicine to recommend at least 150 min of moderate, or 75 min of intense, aerobic exercise per week, as well as strength training at least twice a week to achieve significant health benefits.[75,203,204] In addition, a personalized activity plan may be more effective than a standardized regimen because an individual plan can be customized for different time periods from prediagnosis through cancer treatment based on individual needs and abilities. Perhaps the most important factor affecting breast cancer survivors is long-term compliance with any exercise plan. In order to derive maximum benefit, activity must become integrated into each patient's daily routine to ultimately be successful.

Strength Training & Lymphedema

Lymphedema results from the accumulation of excess fluid in the lymphatic system after breast cancer surgery and/or radiation therapy, and may cause pain, swelling, numbness, stiffness and fatigue in the affected arm.[76] Approximately 30% of breast cancer survivors suffer from lymphedema, which can adversely affect physical and psychosocial wellbeing.[77] Obese patients (BMI > 30) in particular are 3.6-times more likely to develop lymphedema compared with women with a BMI <30, thus the National Lymphedema Network encourages obese women to receive nutrition and weight reduction education.[205]

Risk factors for lymphedema include the number of axillary lymph nodes surgically removed or damaged by radiation, obesity at diagnosis or weight gain after treatment, or activities that irritate or inflame the lymphatic system. In the past, a number of breast cancer advocacy groups such as the ACS, Komen for the Cure, and the National Lymphedema Network recommended limited use of the affected arm to decrease risk of lymphedema. Although these recommendations were designed as risk-reduction strategies, limited use may make daily activities more challenging and actually increase risk of injury.[78]

Two recent randomized clinical trials challenged the widespread recommendation that lymphedema patients should limit use of the affected/at-risk arm. The PAL trial randomized 141 breast cancer survivors with lymphedema and 154 survivors at risk for lymphedema to either a nonexercising control group or to an intervention group who performed progressive weight training twice a week for 1 year. The intervention group showed greater improvements in self-reported symptoms and greater overall strength.[79] Importantly, progressive weight lifting did not exacerbate lymphedema. In at-risk patients who had five or more lymph nodes surgically removed, weight training had a noticeable effect on outcome – 22% of controls developed symptoms of lymphedema compared with only 7% of patients who participated in weight training.[80] Observations that progressive strength training is actually beneficial to patients have revolutionized current concepts of lymphedema treatment and altered current guidelines.[206]

Stress Management

The Effect of Stress on Breast Cancer Prognosis

Psychological distress associated with a diagnosis of breast cancer can evoke an array of emotional experiences, ranging from sadness and despair to anxiety and depression.[81] The shock associated with initial diagnosis, through arduous treatment regimens and ongoing fear of recurrence, can have significant effects on psychological wellbeing.[82] Although emotional symptoms may dissipate, an appreciable number of survivors continue to experience anxiety and depression for years after diagnosis.[83] Psychological stress may elicit a number of physiological changes, including: endocrine responses, which can increase angiogenesis, cell proliferation and migration; disruptions in circadian rhythms and secretion of stress-related hormones such as glucocorticoids and catecholamines; and immune function, resulting in decreased natural killer cell and cytotoxic T-cell activity and increased levels of circulating inflammatory cytokines.[84] Over time, these physiological responses to stress may increase the risk of chronic disease and influence breast cancer mortality.

Epidemiological research suggests that chronic stress due to depression, psychological distress and lack of social support may be a risk factor for breast cancer development and progression. For example, breast cancer survivors who suffered stressful life events, such as divorce, or death of a husband or child, had a significantly higher risk of relapse compared with survivors without such stressors.[85] Women with strong social ties to relatives, friends and neighbors had significantly lower risk of breast cancer mortality compared with women lacking a social network.[86] Similarly, in 2835 women diagnosed with breast cancer, those who felt socially isolated (no close relationships with friends, relatives or adult children) before diagnosis had a 66% increased risk of all-cause mortality and a twofold increase in breast cancer mortality.[87] A meta-analysis indicated that psychosocial stress has an adverse effect on cancer incidence and survival – stressful life experiences were associated with higher cancer incidence, poorer survival and higher cancer mortality.[88]

Stress Reduction & QoL in Breast Cancer Survivors

Group Support In addition to the effects of stress on breast cancer prognosis, a number of studies have examined the impact of stress on QoL in breast cancer survivors. Breast cancer patients often experience social isolation during months of treatment and recovery, which precipitate feelings of loneliness, low self esteem and body image issues, and negatively impact their QoL.[89] Two types of group support have been evaluated for their ability to improve QoL: cognitive behavioral therapy, which uses conversation and active participation to resolve dysfunctional emotions and behaviors in individual or group settings; and psychoeducational therapy, which provides cancer education to patients, teaches coping mechanisms, and offers support and resources to improve psychosocial functioning.[90] Several meta-analyses suggest that these interventions have a positive effect on cancer patients for certain symptoms such as distress, depression, anxiety, fatigue and QoL,[91–94] while other studies conclude that psychosocial interventions are ineffective or limited in producing meaningful emotional benefit.[95–97]

Many studies evaluating the effects of group support in breast cancer patients evaluated the effects of therapy in relatively small numbers of women with wide variability in levels of stress, anxiety and depression at baseline, which may mask the

effects of group support in women with high emotional distress. Despite the inconclusive nature of current research, psychosocial interventions are rapidly becoming an important component of cancer care. For healthcare professionals to provide evidence-based guidance to their cancer patients, high-quality well-controlled trials with predefined outcome measures are needed to determine the precise benefits of psychosocial interventions.

Yoga Yoga is a mind–body therapy that originated in India more than 5000 years ago to reduce stress and promote overall physical and mental wellbeing. The practice of yoga relies on physical postures, focused breathing and meditation to stretch muscles, control breathing and minimize stress through visualization techniques and guided imagery. Cancer survivors, in particular, tend to use CAM approaches such as yoga[98] to alleviate common symptoms including fatigue, pain and insomnia,[99] which may persist long after treatment has been completed.[100–102]

Initial scientific research suggests that yoga may confer a variety of psychological and physical health benefits to breast cancer patients. Small randomized trials have observed significant reductions in fatigue severity, as well as improved vigor and emotional wellbeing following 8–12-week Iyengar yoga interventions.[103,104] A recent meta-analysis of ten studies found that cancer patients participating in yoga showed significantly greater improvements in psychological health, including anxiety, depression, distress and stress, compared with waitlist controls or supportive therapy groups.[105] Breast cancer survivors can improve psychosocial functioning through yoga while they are undergoing active clinical treatment[106] and for years following diagnosis.[107]

Chronic pain and other sequelae such as paraesthesia (burning or tingling sensation of the skin), allodynia (pain caused by light touch) and lymphedema are significantly more frequent in breast cancer survivors compared with women in the general population.[108–110] Yoga has been shown to alleviate various forms of chronic pain experienced by many breast cancer survivors, including lower back pain,[111] pain associated with fibromyalgia[112] and rheumatoid arthritis.[113]

Chronic stress is a common ailment that can negatively impact QoL and survival in women with breast cancer. As an increasing number of women turn to CAM to improve their health after breast cancer diagnosis, it is critical to develop effective methods for managing stress. To date, group support has shown mixed overall results in patients suffering from anxiety and depression, but seems to improve survival in patients with the highest levels of anxiety and depression. Yoga has shown promising results in relieving psychological distress and decreasing fatigue, and may be effective in treating chronic pain associated with side effects of treatment. Most studies to date have been too small to adequately define treatment effects; therefore large-scale studies are urgently needed to quantify the potential benefits of group support, yoga and other measures of stress reduction in breast cancer patients.

Lifestyle Interventions in Patients With Metastatic Breast Cancer

The majority of intervention studies considering the effects of lifestyle factors on breast cancer prognosis may suffer from design limitations that restrict their ability to adequately address survival or recurrence in diverse populations of breast cancer patients.[114] Epidemiologic studies often target women with early-stage breast cancer and do not usually enroll large numbers of patients with late-stage, metastatic disease. Compared with women with localized disease who have a 98% 5-year survival rate, women with stage IV breast cancer have 5-year survival rates of only 23%. Patients living with metastatic disease have different health concerns than women free from metastasis. For example, women with stage IV breast cancer may need bone-strengthening therapy, psychological counseling to deal with social isolation, nutritional counseling to help with appetite and weight loss, treatment for fatigue and pain management. Intervention studies must be tailored to the specific needs of patients with metastatic disease, recognizing that diet, exercise and stress reduction techniques used in other breast cancer survivors may be less desirable or inappropriate.

Despite limited research on patients with metastatic disease, lifestyle interventions have shown emotional benefit in women with stage IV breast cancer. Women randomized to weekly supportive–expressive group therapy demonstrated improved mood and perception of pain,[115] as well as a significantly greater decline in mood disturbance and traumatic stress symptoms compared with controls.[116] Likewise, women randomized to receive cognitive therapy for depression had significantly lower levels of depressive symptoms, anxiety, fatigue and insomnia following treatment compared with those assigned as waitlist controls.[117] Additional studies have shown that other lifestyle interventions, such as yoga-based palliative care, and integrative treatment with nutrition, fitness and mind–spirit instruction improve QoL.[118]

Breast Cancer Studies: Design & Limitations

The complex nature of lifestyle modification and the potential benefit to breast cancer survivors is difficult to assess in human populations, which often leads to contradictory results among studies. The primary study designs outlined in this review include observational studies (prospective cohort studies) and randomized controlled trials. The observational cohort studies followed groups (cohorts) of participants over time (up to ~25 years) to identify associations between lifestyle factors and breast cancer recurrence and mortality.[119] Conversely, randomized controlled trials are considered the gold standard for measuring causality and the efficacy of treatments on breast cancer prognosis.[120] These trials randomly assigned patients with similar characteristics to receive the intervention or to serve as controls who received standard clinical care. At the conclusion of the trials, if a significant difference between the intervention and control groups in recurrence or survival could be detected, this difference was attributed to the intervention.

In general, cohort studies have the advantages of being able to assess multiple aspects of lifestyle and better represent the typical breast cancer patient population; however, as discussed below, potential bias in patient selection and limitations of recall and self-reporting of dietary and physical activity data may have confounded the overall results. Although randomized trials may provide the best evidence of treatment efficacy, these studies are expensive to conduct and thus may not follow patients as long as prospective cohort studies, which may bias estimates of long-term survival and recurrence. In addition, targeted accrual and exclusion of patients with advanced disease, patients undergoing chemotherapy, and patients with evidence of other forms of cancer may restrict the applicability of randomized trials to the general population.

Most of the cohort studies and randomized trials reported here were ethnically homogeneous, containing a large proportion of Caucasian participants, which makes generalizing results to patients with different demographics or genetic backgrounds difficult. Cultural differences in accepting and maintaining lifestyle changes may necessitate alternative intervention strategies for certain groups. Furthermore, a number of published cohort studies as well as randomized trials attempted to evaluate the effects of lifestyle factors in relatively small numbers of women, and thus lacked adequate statistical power to effectively assess potential benefit. The methods of recruitment used to enroll participants in both cohort studies and clinical trials may have confounded the observed relationships between lifestyle factors and outcomes because participants contacted through different media tend to exhibit different disease and motivational characteristics.[121] In the prospective cohort studies utilizing questionnaires to investigate past behaviors, inherent inaccuracies in self-reported data, such as under-reporting caloric intake and overestimating fat reduction[122] due to memory and recall bias is a potentially significant limitation. Randomized trials assessing long-term outcomes such as relapse-free survival are susceptible to contamination bias, where controls begin to engage in lifestyle changes on their own[123] and a gradual erosion of adherence over time occurs,[124] which may impact their ability to quantify the effects of lifestyle changes. As the purpose of this review was to critically weigh the available evidence regarding lifestyle behaviors and breast cancer outcomes, we utilized evidence from both observational studies and clinical trials, which was often complementary, as well as meta-analyses, to derive maximum information on the effects of lifestyle factors on breast cancer prognosis and recurrence.

Conclusions

A multitude of studies investigating the impact of lifestyle modification on breast cancer survivors have produced highly variable and contradictory results. Large-scale dietary studies indicate that specific dietary components may not affect breast cancer mortality, but achieving and/or maintaining a healthy bodyweight through diet provides health benefits to breast cancer survivors. A body of research has definitively linked physical activity to improved prognosis and survival in breast cancer patients. Chronic stress appears to have an adverse effect on breast cancer incidence and survival, particularly in women with the highest levels of anxiety and depression. Although the actual benefits of psychosocial interventions remain controversial, yoga has shown promising effects on psychological health. Lifestyle factors considered in this review are unlikely to exert a uniform influence on outcomes in breast cancer survivors, thus modalities such as physical activity are likely to have a more significant influence than specific dietary components such as green tea or soy. These findings illustrate the need for continued, high-quality research into the effects of lifestyle interventions in breast cancer patients in order to provide survivors with state-of-the-art knowledge and optimum methods for improving long-term prognosis and QoL.

Expert Commentary

As the number of breast cancer survivors increases, interest in lifestyle interventions and CAM approaches continues to grow. Although the main focus for many breast cancer survivors is prevention of disease recurrence, survivors are at increased risk for developing chronic conditions such as osteoporosis, diabetes and cardiovascular disease, as well as noncancer-related mortality.[125] Behavioral modification may provide breast cancer patients with numerous health benefits, both during and after active treatment. In addition to potential health benefits, lifestyle modification may provide patients with feelings of control and self-determination because they become active participants in managing their own health.

Between September 2006 and February 2007, the US President's Cancer Panel examined current evidence regarding the effects of lifestyle behaviors on cancer risk, as well as ways to reduce the national cancer burden by promoting healthy lifestyles.[207] The panel recommended that: healthcare providers coordinate and integrate education and prevention messages related to healthy lifestyles with other chronic diseases to promote common risk reduction strategies; and individuals assume personal responsibility for learning about cancer risk and making healthy lifestyle choices. Research has shown that breast cancer patients who receive healthy lifestyle recommendations, such as a recommendation to exercise, from their oncologist actually participate in these behaviors significantly more than patients following standard treatment;[126] however, only about 25% of patients report actually receiving dietary or physical activity recommendations from their primary care physicians.[127] Healthcare providers must become more involved in recommending (and monitoring implementation of) healthy lifestyle behaviors for their cancer patients. Similarly, breast cancer survivors must be proactive in learning about options for healthier lifestyles and integrating appropriate behaviors into their daily routine.

Despite the large number of studies investigating the effects of lifestyle modification on breast cancer survivorship, few definitive conclusions have emerged. Many lifestyle behaviors may individually affect prognosis, but it is unlikely that a single comprehensive 'lifestyle modification package' is appropriate for all survivors. Patients should consider general 'common-sense' recommendations such as maintaining a healthy weight by consuming a diet rich in plant-based foods and limiting alcohol, being physically active and minimizing stress. Survivors should strive to incorporate as many healthy behaviors as possible, given their individual physical, emotional and financial constraints.

Five-year View

Women with a history of breast cancer constitute the largest group of female cancer survivors, accounting for approximately 22% of all cancer survivors.[208] As the number of breast cancer survivors continues to grow, it is crucial to identify modifiable factors associated with breast cancer recurrence and survival, and to fully understand optimum methods for risk reduction. This information will likely come from a variety of sources but should include well-designed, high-quality randomized trials and observational studies with adequate statistical power – an example is the Pathways study, a prospective study of breast cancer survivorship, which is expecting to enroll 3000 patients within 2 months of diagnosis to reduce the effect of survival-bias.[128] Recruiting women with late-stage disease, who frequently have different physical and emotional needs than early-stage patients, will provide much-needed information for patients with metastasis. Comprehensive clinical programs with research components, such as the Clinical Breast Care Project, a breast cancer research program based at Walter Reed National Military Medical Center (MD, USA), which includes a state-of-the-art comprehensive breast cancer center and research capabilities are vital for examining environmental factors associated with prognosis.[129] Culturally appropriate intervention programs[130] are needed to examine cultural factors that influence behavior modification and ethnic differences in clinical care among survivors from diverse ethnic and socioeconomic backgrounds.[131]

Specific issues of highest priority that need to be resolved over the next 5 years are:

- Who would benefit most from, and thus should participate in, behavioral modification programs? For example, women of advanced age with significant comorbidities or metastatic disease may be unable to participate in certain activity routines or reluctant to adopt new dietary habits;
- Whether an optimum combination of lifestyle choices can be determined on an individual patient basis that provides survival and QoL benefits that are superior to a standardized approach;
- Healthy lifestyle programs need to be developed for a diverse population of breast cancer survivors that have wider adaptability than those presently available;

- Evolution of primary care: medical providers should not discount CAM approaches, given that a majority of patients believe that these alternative therapies improve their QoL. Physicians should be powerful catalysts for promoting behavior change in their patients because they are optimally positioned to deliver guidance regarding health promotion;

- Do interactions between molecular factors and behaviors influence breast cancer recurrence and survival? Identifying genetic variation that may enhance or inhibit responses to lifestyle intervention would add an additional level of personalization to patient care.

Finally, despite the potential benefits of a healthy diet, regular physical activity and stress management, relatively few breast cancer survivors meet commonly prescribed dietary and physical activity guidelines.[132] Research has shown that age[133] and ethnic[134] differences influence the likelihood that survivors will adopt healthy lifestyle behaviors, and patients may not fully adhere over the longer-term to self-directed interventions and may miss potential health benefits.[135] To successfully integrate and sustain healthy behaviors in their daily lives, breast cancer patients must overcome a number of barriers, including ongoing challenges of self-motivation, accessibility to health resources and cost.[136]

Overcoming these barriers will require an infrastructure that includes integration of lifestyle modalities into clinical care (short term) and active community-based programs in both urban and rural settings for longer-term adherence.[137] Further research may allow us to better understand the psychology of self-motivation and adherence in order to optimize mechanisms that mediate successful behavioral change.[138,139] Comprehensive programs such as the STEP program,[140] provided as an adjunct to clinical care, which empower patients to make healthy choices in their daily lives and monitor progress over the long term, are also needed to achieve optimal health and QoL. Adaptations of cardiac rehabilitation models may provide the necessary framework to maximize adherence to dietary and physical activity guidelines. In addition, new paradigms are needed to defray out-of-pocket expenses for implementing healthy lifestyles, such as gym memberships, yoga classes, exercise physiologists and dietician consultations, which may be prohibitive to many breast cancer survivors.[141,142]

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Sidebar

Key Issues

- Due mainly to advances in early detection and treatment, there are an estimated 2.5 million breast cancer survivors in the USA alone, and this number is projected to increase to 3.4 million within the next 4 years. Behavioral modification has great potential to improve prognosis and quality of life in breast cancer survivors.

- Achieving or maintaining a healthy weight after diagnosis is associated with improved prognosis. A healthy diet may not affect breast cancer prognosis but has been associated with increased overall survival.

- Limited research suggests that certain types of alcohol, vitamin supplements, soy and green tea may have some beneficial properties for breast cancer survivors; however, large-scale studies are needed to provide conclusive results and specific recommendations for consumption.

- Moderate physical activity can ameliorate side effects during treatment, and improve breast cancer prognosis and overall survival after treatment.

- Contrary to the long-held belief that patients affected with, or at-risk for, lymphedema should limit use of the affected/at-risk arm, progressive supervised strength training can decrease symptoms and improve outcomes.

- Stress-reduction techniques such as group support and yoga have shown promising results in improving outcomes and quality of life, but further research is essential for quantifying potential benefits in breast cancer patients.
- As more effective healthy lifestyle interventions evolve, important issues such as who will derive the most benefit, when lifestyle interventions should be initiated, how and where programs should be facilitated, and who will pay for healthy lifestyle programs, must be resolved in order for lifestyle modification to have a meaningful impact on the lives of breast cancer survivors.

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Papers of special note have been highlighted as:
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