Lifestyle modifications for patients with breast cancer to improve prognosis and optimize overall health

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Although more than 90% of patients with breast cancer have early stage disease at diagnosis, about 25% will eventually die of distant metastasis.[1] Many patients with breast cancer seek information from a variety of sources about behaviours that may reduce their risk of recurrence.[2] Making positive lifestyle changes can also be psychologically beneficial to patients by empowering them, since the feeling of loss of control is one of biggest challenges of a cancer diagnosis.

In this review, we identify which lifestyle changes can be recommended to patients as an adjunct to standard breast cancer treatments, to reduce their risk of distant recurrence and death. We review the role of lifestyle factors, particularly weight management, exercise, diet, smoking, alcohol intake and vitamin supplementation, on the prognosis of patients with breast cancer. Our literature search is summarized in Box 1.

It is challenging to study lifestyle factors independently, because patients who are more physically active often are leaner, eat a healthier diet and are typically less likely to drink excessive amounts of alcohol or smoke; however, many studies try to adjust for these confounders.[3] Another limitation is the potential impact of lifestyle factors before diagnosis.[4] Regrettably, but understandably, we found very few randomized trials.

How does body weight influence the prognosis for breast cancer?

Women who gain weight during or after treatment of breast cancer have been consistently shown to be at higher risk of breast cancer–related death.[5–7] Also, women who are overweight or obese at the time of diagnosis have a poorer prognosis.[8] Proposed mechanisms of how obesity might affect breast cancer mortality include a rise in circulating insulin-like growth factor, elevated circulating sex hormones and production of pro-inflammatory cytokines.[9–12] Another possible mechanism is metabolic syndrome (presence of at least three of the following five components: abdominal obesity, hypertension, low level of high-density lipoproteins, high plasma glucose level and high triglyceride levels).[13] In a recent study involving early stage breast cancer survivors, patients with metabolic syndrome were at sig-

KEY POINTS

- Physical activity has the strongest effect on reducing the risk of breast cancer recurrence and death.
- All patients with breast cancer (except for those who have an abnormally low body mass index before diagnosis) should avoid gaining weight.
- Patients who are obese and those who smoke have a higher risk of cancer recurrence, but it is unclear whether their prognosis can be improved by weight loss or smoking cessation.
- Soy consumption is not harmful.

nificantly increased risk of distant metastasis (hazard ratio [HR] 2.45, 95% confidence interval [CI] 1.24–4.82) compared with those without the syndrome.[13]

Most patients with breast cancer gain weight both during and after active treatment, and much of the weight is never lost. The average reported weight gain is 2.5–5 kg,[5] but a gain of 10 kg or more is not uncommon.[14] The reasons for weight gain are multifactorial and include "stress eating," reduced activity because of fatigue or other treatment-related adverse effects, lowered metabolic rate from chemotherapy, and use of pre- and post-chemotherapy medications such as dexamethasone.[14] Weight gain is most common in women who experience treatment-related menopause and is often accompanied by relative fat gain and muscle loss.[15]

Several observational studies have shown that gaining weight during or after breast cancer treatment increases the risk of recurrence and reduces survival, irrespective of baseline body mass index (BMI).[5–7] In a recent meta-analysis of 12 studies on weight gain after diagnosis, moderate weight gain (5%–10% of baseline weight) was not associated with increased mortality, but a weight gain of more than 10% was (HR 1.17, 95% CI 1.00–1.38). There was no effect on breast cancer mortality with a weight gain of more than 5% among women with a pre-diagnostic BMI of 25 or higher.[16]

Because being overweight is a risk factor for breast cancer among postmenopausal women, a disproportionate number of women with breast cancer are above their ideal body weight at the time of diagnosis. Over the last five decades, many studies

have shown a higher risk of breast cancer recurrence and mortality among patients who were obese at the time of diagnosis. A meta-analysis of 79 published studies found that, compared with women with a normal weight, those who were obese (BMI > 30) or overweight (BMI 25–30) at diagnosis had significantly higher breast cancer mortality (obese: summary relative risk [RR] 1.35, 95% CI 1.24–1.47; overweight: RR 1.11, 95% CI 1.06–1.17).[8] All-cause mortality was similarly increased. The summary RR for each 5-kg/m^2 increase in baseline BMI was 1.18 (95% CI 1.12–1.25), but substantial heterogeneity was found among the studies. No significant differences were seen between pre- and postmenopausal women. However, in a patient-level meta-analysis of randomized adjuvant studies, increased breast cancer mortality was observed only in the subgroup of heavier premenopausal women with estrogen-receptor–positive breast cancer.[17]

One might then hypothesize that overweight patients who lose weight after a breast cancer diagnosis would have a better outcome. Although multiple studies have shown that weight loss, at least in the short term, is achievable in breast cancer survivors through a variety of strategies,[9,18] there are few data on long-term outcomes.[19] In the randomized Women's Intervention Nutrition Study, which will be discussed later, patients in the dietary intervention arm lost an average of six pounds (2.7 kg) over a five-year period and had a lower incidence of disease recurrence (HR 0.76, 95% CI 0.60–0.98) compared with the control group.[20] However, this difference may have been attributable to the 15% reduction in dietary fat intake in the intervention group.

There is not yet a clear answer regarding the effect of weight loss, or prevention of weight gain, on the prognosis of patients with breast cancer. Two large randomized studies are underway to evaluate the promotion of weight management on breast cancer outcomes.[19,21]

What role can exercise play in improving prognosis?

A recent review of the effect of lifestyle factors on breast cancer mortality concluded that physical activity has the most robust effect of all lifestyle factors on reducing breast cancer recurrence.[22]

Lowered endogenous hormone levels, reduction of inflammation and reversal of insulin resistance have all been hypothesized to mediate the effects of exercise.[23]

A meta-analysis of 22 prospective cohort studies found that breast cancer mortality was significantly reduced among women who reported participating in recreational physical activity after their breast cancer diagnosis (HR 0.59, 95% CI 0.45–0.78). However, there was considerable heterogeneity across studies. The effect was stronger among women who met recommended levels of physical activity (see below), postmenopausal women and women with a BMI greater than 25. In most studies, the effect was independent of the level of activity before the cancer diagnosis.[23] These studies were controlled for baseline BMI; however, weight loss and weight gain were rarely monitored.

Patients should be encouraged to engage in at least 30 minutes of moderate-intensity physical activity at least five days of the week, or 75 minutes of more vigorous exercise, along with two to three weekly strength training sessions, including exercises for major muscle groups. This recommendation has been endorsed by both the Canadian Cancer Society[24] and the American Cancer Society.[25] However, more hours of exercise (but not more vigorous activity) may have increased benefit. Two analyses showed a substantial inverse dose–response effect between hours per week engaged in physical activity and breast cancer mortality.[26,27] Similar beneficial metabolic effects have been shown for both aerobic and resistance exercise, but optimal results are achieved with a combination of the two.[22]

A population-based study in the United States involving 856 women found that only 13% of breast cancer survivors attained the recommended 150 minutes of exercise each week, and with increasing time after diagnosis, only about 10% complied with the recommendation.[28] Patients who have undergone chemotherapy or radiation have significantly greater decreases in physical activity, by 50% and 24% respectively, compared with patients who have not experienced these therapies.[22]

Can a change in diet improve outcomes?

Fats

Preclinical research suggests that excess dietary intake of lipids[29] and carbohydrates can influence metabolic and hormonal processes (e.g., by increasing endogenous estrogen levels) that affect the development of breast cancer metastasis.[30,31] Clinical research is hindered by the variability in diets and the associated metabolic interactions that may occur when trying to study the effects of specific macronutrients. Weight and physical activity can also confound results of dietary studies.

Several observational studies have suggested that high consumption of saturated fats[32] and high-fat dairy products may be associated with an increased risk of breast cancer mortality.[3,33] One study involving 1893 women showed that high intake of high-fat dairy products (> 1 serving daily) was significantly more detrimental than an intake of less than 0.5 servings daily (HR 1.49, 95% CI 1.00–2.24). Low-fat dairy products were not associated with an increased risk of death related to breast cancer.[3] However, BMI and the amount of physical activity may have con-

founded the results of these dietary studies and should be controlled for in future interventional trials.[33]

In the Women's Intervention Nutrition study, in which more than 2400 postmenopausal women with breast cancer were randomly assigned to a dietary intervention (five-year intervention to reduce their dietary fat intake by 15%) or to a control group, the incidence of recurrence was significantly lower in the intervention group (HR 0.76, 95% CI 0.60–0.98).[20] As previously mentioned, it cannot be determined whether this difference was due to the six-pound average weight loss or the reduction in dietary fat intake in the intervention group.

Specific diets

There is currently no particular style of diet that has been found to be more beneficial than another for reducing the risk of breast cancer recurrence.[34] Studies comparing a "prudent" diet (high in fruits, vegetables, whole grains and chicken) to a Western-style diet (high in processed grains, processed meats and red meat) have shown equivalent rates of recurrence.[4,35] In the prospective Women's Health Initiative's Dietary Modification Trial, postmenopausal women with breast cancer who consumed better quality diets (as measured by the validated Healthy Eating Index–2005 calculated from a food frequency questionnaire that was completed an average of 1.5 years after breast cancer diagnosis) did not have a reduced risk of death from breast cancer (HR 0.91, 95% CI 0.60–1.40).[36]

Although a recent meta-analysis did not find a significant effect from a Mediterranean diet (a diet rich in vegetables, unsaturated fats, fruits, fish and whole grains, with moderate red wine intake and limited intake of red meat and simple carbohydrates) on cancer recurrence,[37] several other studies found that a diet similar to the Mediterranean diet (but without the specification to include red wine) had a beneficial effect on breast cancer survival.[37,38] The ongoing prospective DIANA (Diet and Androgens)-5 trial aims to determine whether a Mediterranean diet combined with regular physical activity can improve breast cancer outcomes.[39]

Soy

Many patients are advised by health care professionals, or find information on the Internet, to avoid soy because it contains estrogens. However, findings from clinical studies do not support this recommendation. Soybeans contain both soy isoflavones, which are phytoestrogens, and soy proteins, which can be isolated and extracted. Depending on the extraction process, varying amounts of soy isoflavones can be found in soy protein.[40]

Soy protein isolates increase insulin-like growth factor 1 when consumed in high amounts, which could theoretically promote breast cancer recurrence.[41] One clinical study found that soy protein isolate supplementation caused a slight stimulatory effect on epithelial breast cells in premenopausal women.[42]

Soy products high in isoflavones, such as edamame, tofu, tempeh and miso soup, have been found to have anticarcinogenic effects in preclinical studies, having been associated with apoptosis, antiangiogenesis and reduced sex hormone levels.[41] One study found that supplementation with 200 mg of soy isoflavones daily over two to six weeks before breast cancer surgery showed a non-

significant trend toward inhibition of cancer growth compared with a control group.[43]

A meta-analysis of five prospective cohort studies from the United States and China found that high consumption of soy protein or soy isoflavones after breast cancer diagnosis was associated with a 26% decrease in recurrence (HR 0.74, 95% CI 0.61–0.85) and a 16% reduction in breast cancer mortality (HR 0.84, 95% CI 0.71–0.99) compared with low consumption.[44] Another meta-analysis of four prospective cohort studies, two of which were included in the previous analysis, found a 16% reduced risk of recurrence among women consuming high levels of soy isoflavone (RR 0.84, 95% CI 0.65–0.86), with no significant heterogeneity among the studies.[45] Interestingly, in both meta-analyses, soy intake was not associated with improved survival or reduced recurrence among premenopausal women or patients who used tamoxifen, which suggests that soy and tamoxifen may work through a similar mechanism of displacing estrogen from its receptor.[44] In some studies, the apparent benefit of soy was confined to patients with estrogen-receptor–positive tumours. Phytoestrogens bind to some estrogen receptors to mimic estrogen, whereas others antagonize and block the receptors; however, the selectivity of soy isoflavones is still not well understood.[46]

Although randomized trials would be necessary to confirm that soy intake truly reduces breast cancer recurrence, there is sufficient evidence to at least conclude that soy products need not be avoided. Regardless of whether soy independently reduces recurrence, increasing dietary soy intake may help facilitate weight management if soy products replace higher-calorie sources of protein such as meat.

Is there a benefit from quitting smoking and reducing alcohol consumption?

Recent observational studies have shown that women with breast cancer who have a substantial smoking history have increased breast cancer mortality compared with those who never smoked.[47,48] It is still uncertain whether quitting smoking after a breast cancer diagnosis affects breast cancer recurrence.

In a recent prospective observational study involving 20 691 women with breast cancer, those who continued to smoke after diagnosis (10% of the study population) were more likely than those who never smoked to die of breast cancer (HR 1.72, 95% CI 1.13–2.60),[48] a finding that has been observed by others.[49–52] Compared with women who continued to smoke after diagnosis, those who quit had lower rates of death from breast cancer (HR 0.67, 95% CI 0.38–1.19) and respiratory cancer (HR 0.39, 95% CI 0.16–0.95), but only the latter was statistically significant.[48] The study was well controlled for cancer stage and multiple prognostic factors.

The evidence is not strong enough to overturn the 2014 conclusion of the US Surgeon General that there is insufficient evidence to recommend smoking cessation to reduce breast cancer recurrence.[47] However, there are still several reasons to strongly encourage patients with recently diagnosed breast cancer to quit smoking. These include increased overall mortality among breast cancer survivors who are smokers[53] and an increased risk of venous thrombosis among smokers taking tamoxifen.[54]

Studies of alcohol consumption after a breast cancer diagnosis have not shown a consistent association with disease recurrence. A recent meta-analysis of 14 cohort studies concluded that post-diagnosis alcohol consumption was not associated with breast cancer mortality, although subgroup analyses found that high intake of alcohol (> 20 g/d) was associated with higher breast cancer mortality, with a dose–response association among premenopausal women.[55] A subsequent pooled analysis of four cohort studies reported that alcohol intake of more than one drink daily was associated with a 28% increased risk of late recurrence (> 5 yr after diagnosis) (95% CI 1.01–1.62) among survivors with estrogen-receptor–positive breast cancer.[50] Overall, the results are inconclusive. Nevertheless, limiting alcohol consumption to one or fewer drinks per day is a worthwhile goal to reduce the risk of a second primary breast cancer.[54]

Is vitamin supplementation helpful?

Vitamins C and E

Patients are often told to avoid taking supplements of antioxidant vitamins such as C and E during chemotherapy and radiation because of concerns that these supplements may negate the treatment effects that are mediated, at least in part, by free-radical formation. However, a recent meta-analysis of 10 prospective observational studies of supplemental and dietary vitamin C intake after breast cancer diagnosis (< 400 mg/d in most studies and no more than 1000 mg) found a 15% reduction in breast cancer mortality in the supplement group (summary RR 0.85, 95% CI 0.74–0.99) and a 22% reduction for a 100-mg/d increase in dietary vitamin C (summary RR 0.78, 95% CI 0.64–0.94).[56] These studies did not correct for BMI, use of other supplements, other dietary components or physical activity. There was no clear detrimental effect of vitamin C taken during chemotherapy or radiation. Randomized trials to confirm these findings are warranted.

Most studies have not found an association between vitamin E supplementation and reduced breast cancer recurrence or breast cancer mortality.[57,58]

Vitamin D

Low levels of 25-hydroxyvitamin D may be associated with an increased risk of death from breast cancer.[59,60] Vitamin D exhibits pro-differentiation and anti-proliferation properties.[12]

A meta-analysis of six prospective studies, including cohort and nested case–control studies, found that higher 25-hydroxyvitamin D levels were associated with a lower risk of breast cancer mortality (pooled RR 0.58, 95% CI 0.40–0.85), with no evidence of heterogeneity.[61] Each 10-ng/mL (25-nmol/L) increment in blood 25-hydroxyvitamin D levels was associated with a 0.88 relative risk in breast cancer mortality (95% CI 0.79–0.98) and a 0.84 relative risk in overall mortality (95% CI 0.78–0.91). The association with supplemental vitamin D was only slightly stronger than dietary intake of vitamin D.

Another meta-analysis of five studies showed that higher serum 25-hydroxyvitamin D levels at diagnosis were associated with lower breast cancer mortality.[62] Patients with vitamin D levels in the highest quintile had about half the death rate of those with levels in the lowest quintile (HR 0.56, 95% CI 0.40–0.70). Two earlier studies showed that higher vitamin D intake was associated with a lower risk of recurrence among premenopausal patients (p = 0.02)[63] and among patients with estrogen-receptor–positive tumours (p = 0.01).[58] Moreover, a retrospective study involving patients with HER2-positive breast cancer showed significant improvement in disease-free survival among those given trastuzumab and a vitamin D supplement (< 1500 IU/d) (HR 0.36, 95% CI 0.15–0.88) compared with patients receiving the same treatment without a vitamin D supplement.[64]

Monitoring serum 25-hydroxyvitamin D levels in breast cancer patients may be prudent, with a goal of maintaining a concentration within the normal range of 30–80 ng/mL (75–200 nmol/L).[62] Although randomized clinical trials are warranted to confirm the effect of vitamin D supplementation on breast cancer survival, there are other reasons to optimize patients' vitamin D levels. Chemotherapy, tamoxifen and ovarian suppression all reduce the bone density of premenopausal women, and aromatase inhibitors lower bone density and increase the risk of fractures, particularly in postmenopausal women.

Multivitamins

A review of four cohort studies on multivitamin supplementation after breast cancer diagnosis found no association with breast cancer recurrence or breast cancer mortality. However, the subgroup of patients with estrogen-receptor–negative disease had a 25% reduced risk of recurrence with multivitamin supplementation after diagnosis (HR 0.75, 95% CI 0.59–0.95).[58]

Which lifestyle modifications should be encouraged?

A summary of key findings is presented in Box 2.

Of all lifestyle factors, physical activity has the most robust effect on breast cancer outcomes. Following the recommended 150 minutes of moderate to vigorous exercise or 75 minutes of vigorous exercise per week, along with two to three weekly sessions of strength training, can help reduce the risk of breast cancer recurrence and mortality. Because it is common for patients to reduce their level of physical activity after a breast cancer diagnosis, it is important for health care professionals to promote and encourage exercise in this patient population. Simply receiving advice from an oncologist to exercise more has been shown to increase patients' level of physical activity.[65] Although cancer centres are increasingly developing short-term exercise programs for their patients, primary care providers have an essential role in reinforcing the need to turn exercise into a life-long habit. Some experts have recommended having systems in place to refer patients directly from a cancer care clinic to community-based exercise programs specialized for cancer survivors.[66] Although specific exercise interventions can result in strong behavioural changes, providing support to patients by phone or email has also proven effective.[67]

Weight gain of more than 10% body weight after a breast cancer diagnosis increases breast cancer mortality and all-cause mortality. However, there are good reasons to discourage even moderate weight gain because of its negative effects on mood and body image.[68] Again, physical activity is key. Women who participate in an aerobic exercise program while undergoing adjuvant chemo-

therapy generally do not gain weight, whereas those who do not exercise gain 3.2 kg on average.[5] The benefits of exercise extend well beyond effects on prognosis, including substantial self-perceived improvements in appearance, cardiorespiratory fitness, lymphedema and emotional well-being.[22]

Obesity at diagnosis has a negative impact on breast cancer prognosis, but it is still unclear whether weight loss improves the prognosis of overweight and obese women.

Patients should be strongly encouraged to quit smoking to improve overall survival and possibly breast cancer–specific sur-

vival.[47] Presenting evidence to patients who smoke that it's not too late to benefit from quitting,[47,69] carefully monitoring patients' smoking status at each visit, and recommending pharmacologic or behavioural therapy[70] are all strategies that can aid patients with smoking cessation.

There is no evidence to support a recommendation that patients with breast cancer refrain from eating soy products; increasing intake of soy products may be protective.

Randomized trials are needed to confirm whether decreased intake of saturated fat (especially dairy fat), increased soy consumption, moderation of alcohol intake, and increased vitamin C or D supplementation can reduce breast cancer mortality (Box 3). Results of ongoing interventional studies are eagerly awaited. In the meantime, most patients would benefit from vitamin D supplementation, at least to optimize bone health.

An important point to emphasize is that lifestyle changes, although often protective, cannot always improve outcomes of cancer with particularly aggressive biology. Patients should not be made to feel that inadequate lifestyle changes have led to recurrence of their cancer.

Although most patients with breast cancer die from other causes, a cancer diagnosis creates a "teachable moment" when patients are more receptive to healthy lifestyle changes. Regardless of whether these changes affect the prognosis, they will almost certainly improve patients' overall health.

Box 2: Summary of key findings

Weight management

- Weight gain during or after breast cancer treatment increases the risk of recurrence and reduces survival, irrespective of baseline body mass index.[5–7]

- Patients who are obese or overweight at breast cancer diagnosis have a poorer prognosis.[8] Although it is possible for such patients to attain meaningful weight loss,[9,18] there are few data on whether this improves breast cancer outcomes.[19]

Physical activity

- Physical activity can reduce breast cancer mortality by about 40%[23] and has the most powerful effect of any lifestyle factor on breast cancer outcomes.[22]

- At least 150 minutes per week of physical activity is recommended,[24,25] but less than 13% of patients with breast cancer attain this.[28]

Diet

- Western-style diets (high in processed grains, processed meats and red meat) and prudent diets (high in fruits, vegetables, whole grains and chicken) have similar rates of breast cancer recurrence.[4,35]

- Dietary saturated fat, especially from high-fat dairy products, may be associated with increased breast cancer mortality.[3,32,33]

- Soy products have not been found to increase breast cancer recurrence[41] and may actually reduce it.[44,45]

Smoking

- Recent evidence has shown a strong association between a history of smoking and breast cancer mortality.[47]

- Compared with women who continue to smoke after a breast cancer diagnosis, those who quit smoking after diagnosis have higher overall survival and possibly better breast cancer–specific survival.[48–52]

Alcohol intake

- Findings are too inconsistent to conclude that alcohol consumption affects breast cancer outcomes. However, limiting alcohol consumption to one or fewer drinks per day reduces the risk of a second primary breast cancer.[54]

Vitamin supplementation

- Moderate increases in dietary vitamin C or oral supplementation may reduce breast cancer mortality,[56] but randomized trials are needed to confirm these findings.

- Vitamin E supplementation is not associated with breast cancer outcomes.[57,58]

- Low levels of serum 25-hydroxyvitamin D at diagnosis have been associated with an increased risk of breast cancer mortality.[59–62] However, randomized trials are needed to determine whether supplementation improves prognosis.

Box 3: Unanswered questions

- Does weight loss after diagnosis improve survival for obese/overweight patients?

- Can a reduction in dietary saturated fat or high-fat dairy products improve prognosis?

- Are soy isoflavones protective against recurrence?

- Does quitting smoking after a breast cancer diagnosis decrease breast cancer mortality?

- What should the weekly limit of alcohol consumption be for patients with breast cancer?

- Does vitamin C or D supplementation reduce the risk of distant recurrence?

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