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Nutrition and Survival After the Diagnosis of Breast Cancer : A Review of the Evidence

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Abstract

Purpose—To review and summarize evidence from clinical and epidemiologic studies that have examined the relationship between nutritional factors, survival, and recurrence after the diagnosis of breast cancer.

Materials and Methods—Relevant clinical and epidemiologic studies were identified through a MEDLINE search. References of identified reports also were used to identify additional published articles for critical review.

Results—Several nutritional factors modify the progression of disease and prognosis after the diagnosis of breast cancer. Overweight or obesity is associated with poorer prognosis in the majority of the studies that have examined this relationship. Treatment-related weight gain also may influence disease-free survival, reduce quality of life, and increase risk for comorbid conditions. Five of 12 studies that examined the relationship between dietary fat and survival found an inverse association, which was not evident on energy adjustment in most of these studies. The majority of the studies that examined intakes of vegetables or nutrients provided by vegetables and fruit found an inverse relationship with survival. Alcohol intake was not associated with survival in the majority of the studies that examined this relationship.

Conclusion—Much remains to be learned about the role of nutritional factors in survival after the diagnosis of breast cancer. Healthy weight control with an emphasis on exercise to preserve or increase lean muscle mass and a diet that includes nutrient-rich vegetables can be recommended. Diets that have adequate vegetables, fruit, whole grains, and low-fat dairy foods and that are low in saturated fat may help to lower overall disease risk in this population.

THE HIGH INCIDENCE of breast cancer coupled with improvements in initial treatments have lead to an ever-increasing number of breast cancer survivors.[1,2] Recurrence is an important issue in the management of these patients,[3] but so too are risks for second primary cancers, diabetes, cardiovascular disease, and osteoporosis, because these patients are at increased risk for these comorbidities.[4,5] For many of these disorders, the benefit of dietary intervention or weight management has a demonstrated role.[4,5]

Although cancer places individuals at increased risk, life-threatening events also can serve as powerful agents to promote lifestyle change.[6] Studies conducted among women who have been diagnosed with breast cancer consistently indicate that a majority are interested in making healthful changes in their diets.[7–10] A study conducted among 531 breast cancer survivors also found that 52% of patients wanted nutritional guidance at the time of diagnosis or soon

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after, although few reported having ever received dietary recommendations from their physicians.[8]

Thus, women who have been diagnosed with breast cancer are highly motivated to pursue dietary regimens and often seek nutritional guidance. Indeed, the opportunity exists for the clinician to take advantage of this interest or "teachable moment" to reinforce various components of an optimal diet aimed at promoting health in both the short and long term. Given the central role of oncologists and the credence placed on their advice, the delivery of health messages aimed at improving diet may be especially meaningful.[11] However, what are the recommendations that can be supported by the current evidence?

Over the past several decades, a considerable amount of research has explored the possible relationships between various nutritional factors and the risk for breast cancer. In contrast, there are far fewer data on associations between nutritional factors and progression or recurrent disease. The purpose of this article is to review and summarize evidence on the relationship between nutritional factors and survival after the diagnosis of breast cancer— evidence based on review of recent clinical and epidemiologic studies—in order to suggest clinically useful guidelines and strategies for patient management.

MATERIALS AND METHODS

Relevant clinical and epidemiologic studies of nutritional factors, survival, and disease recurrence in women who had been diagnosed with breast cancer were identified through MEDLINE search; MeSH keywords included the following: breast cancer, survival, prognosis, body weight, body fat, anthropometry, weight gain, diet, dietary intakes, nutrition, and nutritional status. References of identified reports also were used to identify further articles for critical review. In addition to the focus on epidemiologic or clinical (human) studies, we applied additional inclusion criteria. Only reports that linked nutritional factors to disease-free or overall survival, recurrence, or both were included, and we excluded studies of associations between nutritional factors and intermediate end points or tumor characteristics at diagnosis. Only articles written in the English language were included.

The two major nutritional issues that have been addressed in relation to survival are relative body weight (or indicators of obesity) and diet composition. Studies published between 1985 and February 2002 were critically reviewed. Given that a critical review and analysis of the association between overweight and survival had been reported by Goodwin and Boyd[12] in 1990, this served as a benchmark, and review with regard to this topic was limited to subsequent articles published between 1990 and February 2002.

BODY WEIGHT, OBESITY, AND SURVIVAL

Obesity at Diagnosis and Survival

The critical review and analysis by Goodwin and Boyd[12] of 13 cohort studies and one case control study on the association between obesity at diagnosis and prognosis published in 1990 concluded that increased body weight exerts a negative, albeit modest, prognostic effect. Since that time, 26 published studies have examined associations either between premorbid weight status or weight status at the time of diagnosis (estimated by relative weight for height or body mass index [BMI], expressed in kg/m^2]), and breast cancer recurrence and survival. A critical review on this topic, from a slightly different perspective, also was reported by Chlebowski et al.[13] A summary of these studies[14–39] is listed in Table 1. In 17 of the 26 studies, increased BMI or body weight was found to be a significant risk factor for recurrent disease, decreased survival, or both[14–30]; seven studies produced null findings[31–37]; and two studies found a significant inverse association between weight status and recurrence.[38,39]

In those studies that found a significant positive association between overweight and progressive disease, women categorized in the higher (*v* lower) levels of obesity exhibited a 30% to 540% increased risk of death. Furthermore, analysis of the data suggests that this relationship may be more pronounced among women who are diagnosed initially with early-stage disease[17,28] and among those who have estrogen receptor-positive tumors.[15] It also should be noted that similar to many other chronic diseases, the relationship between body weight and disease progression may be curvilinear rather than linear. More research, especially studies in which the effect on risk is controlled for important influencing factors, such as smoking status and hypertension, are necessary to confirm a curvilinear association, or a J-shaped curve.[40]

Given that upper body fat distribution has been linked with higher unbound levels of sex hormones[41] as well as insulin,[42] upper body or android obesity also has been implicated as a risk factor for several diseases,[43] including breast cancer,[44] with speculation that android obesity may portend greater risk for mortality. In a study of both pre- and postmenopausal patients by Kumar et al,[38] android body fat distribution, as indicated by a higher suprailiac:thigh ratio, was found to be a significant negative prognostic indicator, even though higher BMI status was protective. These findings contrast with those of Zhang et al,[19] who found no association between android obesity, as indicated by a greater waist-to-hip ratio, and survival, but who did detect a significantly greater risk of death among women in the top tertile of BMI.

A notable feature of these studies is that the effect of obesity on prognosis was examined by using premorbid weight or weight at diagnosis. It is currently unknown whether postdiagnosis weight reduction through diet, increased physical activity, or both modifies this relationship.

Weight Gain After Diagnosis

Unfortunately, weight gain often occurs in women after diagnosis of breast cancer; such weight gain is more prevalent among women who were premenopausal at diagnosis and who received adjuvant chemotherapy as part of their treatment.[45] Other factors found to be positively and independently associated with postdiagnosis weight gain are African-American ethnicity and current energy intake.[46] Prediagnosis BMI, age at diagnosis, level of education, and usual exercise level also have been found to be inversely associated with weight gain.[46] Gains in weight usually range from 2.5 to 6.2 kg; however, greater gains are not uncommon.[45]

There is some evidence to suggest that weight gain after diagnosis adversely affects disease-free survival. Camoriano et al[21] observed 646 patients with breast cancer for a median of 6.6 years and found that women who were premenopausal at diagnosis and who gained more than the median amount of weight (5.9 kg) were 1.5 times more likely to relapse and 1.6 times more likely to die of their breast cancer. Results from a study by Chlebowski et al[47] parallel these findings. In contrast, two other studies failed to identify any association between postdiagnosis weight gain and prognosis.[48,49] These studies are more than 10 years old, and analysis of more current data are needed to define associations, if any, between postdiagnosis weight gain and survival.

Although it remains to be determined whether postdiagnosis weight gain influences risk for progressive disease, it is known that weight gain adversely affects risk for cardiovascular disease and diabetes, conditions for which women who have been diagnosed with breast cancer are at already at increased risk.[4,5] Furthermore, several studies indicating that patients find weight gain distressing have been reported since 1983.[49–54]

The relationship between psychologic characteristics and weight gain have been examined in two studies. Dietary restraint and disinhibition, two characteristics of dieting behavior, were

highly associated with both short-term (6 months after diagnosis) and long-term (19 months after diagnosis) weight gain (n = 73).[50] In another study conducted among 56 women with breast cancer and 52 healthy women, BMI was found to be directly associated with greater depressive symptomology and abnormal eating attitudes and behavior.[55] Thus, depression, eating pathology, and difficulty maintaining a desirable weight seem to be interrelated; however, from cross-sectional studies, it is impossible to determine whether depression and eating pathology beget problems with weight control or vice versa.

The weight gain that women who have been diagnosed with breast cancer experience—at least, those who receive adjuvant chemotherapy—also seems unique. Although typical weight gain is usually characterized by a gain in lean tissue as well as adipose tissue, all clinical studies that have measured body composition change, either via computed tomography, dual energy x-ray absorptiometry, or in vivo neutron capture, have consistently found either no gains in lean tissue mass or actual losses in lean tissue mass as weight and adipose tissue increase in women after the diagnosis of breast cancer.[56–60] This unique type of weight gain also is manifest with conditions such as hypogonadism, hypopituitarism, and chronic physical inactivity, as well as corticosteroid use. In addition, gradual body composition changes such as these are noted during the 10-year period encompassing menopause; however, among premenopausal patients treated with chemotherapy, this aspect of aging seems to be accelerated, and these same changes in body composition are observed within the span of 1 year.[59]

Interventions to Reduce Weight Gain or Promote Weight Loss

Few interventions have been devised and tested specifically during the time when weight gain seems to be the most problematic (ie, within the year after diagnosis).[45] In one report, intensive diet counseling aimed at weight maintenance produced small but insignificant reductions in energy intake and weight gain among 107 women receiving adjuvant chemotherapy for resected breast cancer.[61] Likewise, insignificant differences in weight gain were observed in a small study by Winningham et al,[62] in which 24 early-stage breast cancer patients receiving adjuvant chemotherapy were randomized into a group that was instructed to pursue routine aerobic activity versus a sedentary control group; gains in weight were 0.82 *v* 1.99 kg, respectively (not significant). In this study, however, significant differences were observed in the change in percentage of body fat (averaging −0.51% in the experimental group *v* +2.19% in the control group) during the study period.

In two small intervention studies that incorporated both dietary guidance and increased physical activity, a significant reduction in body weight in overweight women (or weight maintenance in those not overweight) was observed.[63,64] Aerobic exercise was identified as the strongest predictor of success when the intervention components were analyzed for independent effects on weight loss.[63] Other studies testing various approaches to promoting weight loss or weight maintenance in women after the diagnosis of breast cancer are under way.

Possible Mechanisms

Several mechanisms have been proposed to explain the adverse effect of excess adiposity on prognosis after the diagnosis of breast cancer. One proposed mechanism relates to the effect of excess adipose tissue on circulating gonadal hormones because adipose tissue serves as an important extragonadal source of estrogens from precursor adrenal androgens.[65] In laboratory animal experiments, estrogens have been demonstrated to promote breast tumorigenesis.[66] As has been reviewed recently,[65] current evidence generally supports the hypothesis that gonadal hormones play some role in the initiation and promotion of breast cancer, although the relationship seems to be complex. Also, antiestrogen therapy has emerged as one of the most effective treatments for the management of endocrine-responsive breast cancers, which

account for approximately two thirds of cases, as demonstrated in clinical trials.[67–69] Obesity is consistently associated with increased circulating concentrations of estrone and estradiol in postmenopausal women, and more importantly, it is associated with decreased levels of sex hormone–binding globulin, which results in an increase in the bioavailable estrogen fraction.[70,71]

Another possible mechanism relates to insulin and insulin-like growth factor 1 (IGF-1) and the interactions of these factors with adiposity and weight gain.[72,73] In cell culture studies, insulin and IGFs exhibit mitogenic effects that influence both premalignant and cancerous stages of cell growth.[74] Both insulin and IGF-1 stimulate the synthesis of sex steroids, and thus their cancer-promoting effects in the progression of breast cancer may be mediated by an effect on gonadal hormones. Evidence from epidemiologic and clinical studies suggests that increased BMI in women is associated with increased insulin and IGFs, characteristics that are associated with increased risk or progression of breast cancer in some,[30,73,75] but not all,[76] studies.

Another explanation for poorer survival among those who are obese at the time of diagnosis has been offered by Madarnas et al,[77] who speculate that the disease of obese women may fail to respond to treatment as a result of the common practice of chemotherapy capping at a body-surface area of 2 m^2, which may offer suboptimal treatment benefit. Their data suggest that this problem may be further compounded by significantly greater dose reductions among women with BMI ≥ 25 kg/m^2 in which the mean dose reduction was 6.7% ± 13.1%, as compared with women with BMIs less than 25 kg/m^2, where the mean dose reduction was 4.3% ± 8.2% (P = .008).

DIET COMPOSITION AND SURVIVAL

Prospective Studies

During the past two decades, the relationships between overall survival or recurrence and dietary intakes have been examined in 13 studies involving cohorts of women who had been diagnosed with breast cancer.[19,25,36,78–87] The dietary factors examined in these studies were mainly those associated with breast cancer risk. These studies are summarized in Table 2. As noted in Table 2, most of these studies used dietary data collected at the time of diagnosis or soon thereafter.

In these and other epidemiologic studies, food intake is self-reported and should be interpreted as estimates that may allow ranking rather than producing absolute values, even when the best-developed methodologies are used. Thus, a high risk for reporting bias and misclassification of subjects is inherent in this type of research. As noted in Table 2, several different methodologies were used to collect the dietary data in these studies, with self-administered food-frequency questionnaires being the most common method used. In the majority of the studies, dietary data were collected immediately after diagnosis, although the participants were often asked to report intake during the year preceding diagnosis. Associations between dietary factors, survival, and recurrence should ideally be adjusted for the effects of major nondietary determinants of survival, such as stage of cancer at diagnosis. This analysis strategy was used by some, but not all, of these studies. For the studies that analyzed associations with and without adjustment for stage and other possible influencing factors, the results summarized are the associations between dietary intake, survival, and recurrence adjusted for stage and other influencing factors.

The possible link between dietary fat and primary breast cancer risk has historically been the focus of more attention than other dietary factors, so fat intake (or selected high-fat foods) were examined in all of these studies. In addition to the general concerns described above, a major issue in the interpretation of the data relating dietary fat intake to breast cancer risk or

progression is that fat intake and total energy consumption always covary (and also typically correlate with obesity), so an independent effect of total dietary fat per se is difficult to accurately assess unless the analysis is adjusted for these factors. Also, self-reported dietary assessment is known to underestimate energy intake, and this bias is most evident for high-fat foods.[88,89] Underreporting affects the accuracy of dietary data more among women (*v* men), those categorized as overweight, minority groups, and younger (*v* older) adults.[90] Rates of underreporting of intake among breast cancer survivors are similar to rates in the general population, with obese women being twice as likely as nonobese women to underreport intake.[91] To minimize the bias introduced by underreporting, particularly in the interpretation of data on fat intake, adjustment for energy intake is the accepted approach used in the analysis of associations between dietary fat and disease risk.[92]

Total dietary fat intake was significantly inversely associated with survival or treatment failure (described as recurrence or new cancer of the contralateral breast) in five of the 12 studies that examined this relationship,[19,36,79,81,84] although the relationship with fat intake was unadjusted for energy intake in three of these five reports.[19,79,81] In one of these studies, this relationship was seen only in women with estrogen receptor–positive (but not negative) tumors.[84] A trend for this relationship was observed in another study.[85] In two studies in which the investigators also analyzed fat intake as an energy-adjusted variable, adjusted fat intake was unrelated to survival.[19,36] In a study in which the intakes of selected foods (rather than nutrients) were examined in relation to recurrence or risk for death,[25] intakes of butter, margarine, and lard were directly associated with risk of recurrence but not with risk of death.

In 10 of these studies,[19,36,78,80,81,83–87] intakes of various types of fat (in addition to total fat intake) were examined in the analysis. Studies in which total fat intake was not associated with survival or recurrence generally found no relationship between survival and intakes of various types of fat, with one exception. Jain et al[78] found energy-adjusted saturated fat intake (but not total fat intake) to be significantly inversely associated with survival. In two of the studies in which total fat intake was associated with survival, intake of a fat subtype also was found to be similarly associated. Holm et al[84] found both energy-adjusted total and saturated fat intakes to be directly associated with risk for recurrence or new cancer, and Zhang et al[19] found monounsaturated fat intake (in addition to total fat intake), unadjusted for energy intake, to be inversely related to survival. In women with node-negative disease, a protective effect of omega-3 fatty acid intake was observed in one study.[87] Thus, these studies do not provide strong support for a role for specific fat types in breast cancer progression.

Results of the analysis of associations between vegetable intake (or nutrients provided by vegetables and fruit, such as carotenoids and vitamin C) suggest a protective effect, although the strength of the association is modest. Of the eight studies that examined these dietary factors,[19,36,78,82,84–87] three found a significant inverse association with risk of death,[78,85,86] one found that risk of dying was nonsignificantly decreased in association with frequent vegetable consumption,[82] and one found a significant inverse association in women with node-negative disease, who comprised 62% of that cohort (but not in the total group that included women at all stages of invasive breast cancer).[87] In the studies that found an inverse relationship with survival and intakes of vegetables, fruit and related nutrients (beta-carotene, vitamin C), the magnitude of the protective effect was a 20% to 90% reduction in risk for death. Given that there is some variability in the findings and in the vegetable-related dietary factors that have been examined in these studies, these data do not provide conclusive evidence for a beneficial effect. Further research that examines the association between survival and intakes of vegetables and the various constituent phytochemicals would be useful.

The relationship between dietary fiber intake, survival, and recurrence was examined in seven of these cohorts of breast cancer survivors.[19,36,78,84–87] None of these studies found a

significant relationship in the total group under study, although the point estimates in one study suggest a trend for a protective effect.[84] In four studies, intakes of selected high-fiber foods (ie, vegetables, fruits, cereal-grain products) were examined in relation to survival, recurrence, or both.[36,82,86,87] As noted above, a significant protective effect of vegetables and fruit was found in one study,[86] one found a trend for this relationship,[82] and one found a protective relationship in women with node-negative disease.[87] Bread and cereal intake was inversely associated with risk for recurrence in one of the three studies that specifically examined the relationship between survival and recurrence and this food type.[36]

Another dietary factor of interest in this patient population is alcohol, which has been consistently and positively associated with risk for primary breast cancer in epidemiologic studies.[93] In the eight studies that examined the relationship between alcohol intake and survival in women who had been diagnosed with breast cancer,[19,36,78,82,84–87] no significant associations were observed, although one of these studies reported that risk of dying was slightly (but not significantly) increased in association with frequent alcohol consumption.[82] In the study involving the analysis of relationships that were based on selected foods rather than nutrients,[25] the consumption of beer, but not wine or liquor, was inversely associated with risk of recurrence but was not associated with risk of death. These findings are fairly consistent and suggest that alcohol intake may not increase risk for recurrence or overall survival after the diagnosis of breast cancer.

To date, no epidemiologic or clinical studies have examined or reported the relationship between soy intake and survival in women who have been diagnosed with breast cancer. Also, studies conducted to date have not identified dietary supplement use as being protective against recurrence in breast cancer survivors.

Possible Mechanisms for Dietary Factors

Various mechanisms by which dietary fat may promote increased risk for and progression of breast cancer have been previously reviewed.[94–96] In animal studies, diets that are rich in linoleic acid (an omega-6 fatty acid) have been observed to promote tumor development in rats exposed to a mammary chemical carcinogen, possibly by a mechanism that involves tumor cell eicosanoids.[96] Free-radical mediated lipid peroxidation and DNA-adduct formation has also been suggested to be another mechanism by which dietary fat could promote carcinogenesis.[94] Clinical studies have suggested that low-fat diets may decrease serum estrogen concentrations, as reviewed and summarized in a meta-analysis.[97] However, significant weight loss also occurred in response to the low-fat diet modification in the majority of the studies in which serum estradiol was significantly reduced in response to a low-fat diet intervention, and an energy deficit and weight reduction would be expected to produce a reduction in serum gonadal hormone concentrations independent of diet composition. In fact, the promotion of weight loss is another proposed mechanism by which lower fat intake could influence the progression of breast cancer.[95]

Several biologically feasible mechanisms that might explain a protective effect of vegetables and fruits have been demonstrated in cell culture and animal studies. For example, carotenoids have retinoid-like effects on cellular differentiation and apoptosis and also exhibit inhibitory effects on mammary cell growth.[98–100] Vegetables of the *Brassica* genus, such as broccoli, demonstrate a favorable effect on estrogen metabolism via the induction of cytochrome P-450.[101] In mammalian biologic systems, fiber binds estrogen in the enterohepatic circulation and interferes with reabsorption, thus reducing circulating estrogen concentrations.[102,103]

Diet Intervention Trials

Two large multicenter randomized controlled trials are examining whether diet modification can influence the risk for recurrence and survival after the diagnosis of early-stage breast cancer. In both of these studies, participants will be followed up for an average of at least 6 years, and results are anticipated after 2005.

The Women's Intervention Nutrition Study (WINS) involves 2,500 postmenopausal women who were randomized within 12 months of primary surgery for breast cancer, and the goal of the intervention is a reduction in dietary fat intake (≤ 15% energy from fat). The rationale for the WINS is based on comparisons of survival of women diagnosed with breast cancer across countries with different fat consumption patterns and evidence from cell culture and laboratory animal studies suggesting that dietary fat may affect a variety of factors involved in the progression of breast cancer.[94,104]

The WINS pilot and feasibility studies demonstrated that women with postmenopausal breast cancer would adhere to a low-fat diet and suggest that hormonal factors may be responsive to the dietary change. In a 6-month feasibility study, 19 of 27 postmenopausal breast cancer survivors completed the counseling sessions, with average fat intake reduced from 34% to 22% of energy, body weight reduced by an average of 2.3 kg, and serum estradiol (but not estrone) reduced by 37%.[105] In a report of data from 93 women enrolled onto the feasibility phase of WINS, the low-fat diet intervention was associated with a reduction in fat intake to 21% of energy, an average weight loss of 2 kg, and an average 20% reduction in serum estradiol concentrations in subjects with baseline serum estradiol ≥ 10 pg/mL at 6 months after randomization.[106] Subjects with lower serum estradiol concentrations at baseline exhibited a significant increase in serum estradiol in response to the intervention, and serum estrone, estrone sulfate, and sex hormone– binding globulin concentrations did not change in that study. In another subset of 290 WINS feasibility study subjects, fat intake was significantly reduced in the intervention group versus the control group (averaging 20% *v* 32% of energy) at 3 months.[107]

In the Women's Healthy Eating and Living (WHEL) study, the participants are 3,109 pre- and postmenopausal women who were enrolled onto the trial and randomized after completion of initial therapies and within 4 years of diagnosis.[108] The primary emphasis of the WHEL study diet intervention is on increased vegetable and fruit intake, with daily dietary goals of five vegetable servings, 16 ounces of vegetable juice, three fruit servings, 15% to 20% energy from fat, and 30 g of dietary fiber. The rationale is that a high-vegetable, high-fiber diet may influence progression of breast cancer through several mechanisms. For example, this dietary pattern may exert beneficial effects on gonadal hormones, and increased intakes of carotenoids provided by vegetables and fruit may promote normal mammary cell growth regulation.[98–100] Other biologic activities of phytochemicals, such as antioxidant activity, also are hypothesized to contribute to beneficial effects of a plant-based diet on risk for cancer progression.

In the WHEL feasibility study that involved 93 women, intervention group subjects increased vegetable intake more than two-fold, from 2.8 to 7.4 servings per day, at 12 months.[109] These subjects also significantly increased mean intakes of fruit (from 2.9 to 4.0 servings per day) and fiber (from 12.8 to 21.0 g/1,000 kcal/d) and reduced fat intake from 29% to 20% of energy. Plasma carotenoids, a biomarker of the high vegetable and fruit intervention, were increased nearly two-fold in the first 12 months of the feasibility study and remained significantly higher in the intervention group versus comparison group at 3 years after randomization.[110,111]

CLINICAL IMPLICATIONS

The position of the American Cancer Society is that the dietary guidelines for cancer prevention can form the basis of nutritional guidance for women who have been diagnosed with breast cancer.[112,113] Given current evidence, a recommendation that may be particularly helpful for this target population is encouraging healthy weight control with an emphasis on exercise to preserve or increase lean body mass. Current recommendations for successful weight management include dietary therapy, increased physical activity, behavior therapy to promote sustained changes in lifestyle, and ongoing monitoring of progress.[114] Also, a diet with nutrient- and phytochemical-rich vegetables, which provides an adequate intake of multiple constituents such as vitamins, fiber, and various potentially beneficial biologically active compounds, may be beneficial. Results from ongoing randomized clinical trials, which are expected within the next few years, are anticipated to expand our knowledge base in this area considerably.

The risk of morbidity and mortality from causes other than breast cancer should be considered when making dietary recommendations for breast cancer survivors, especially those diagnosed with early-stage cancers. For example, even though evidence to support a link between fat intake and breast cancer risk and prognosis is not strong, limiting saturated fat intake is a well-established strategy to reduce risk for cardiovascular disease.[115] Diets that emphasize vegetables, fruit, whole grains, fiber, and low-fat dairy foods and that are low in saturated fat are advised as a prudent strategy to promote health and prevent disease.[116] This dietary pattern has specifically been associated with decreased risk of all-cause mortality in women.[117] Sufficient dietary calcium, adequate vitamin D, and increased physical activity are particularly appropriate recommendations to maintain bone health in these women.

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Table 1

Findings From Studies (1990–2002) of Associations Between Overweight or Obesity and Prognosis

Study	Sample (size and key characteristics)	Years of Follow-Up	Time Point of Weight Status Indicator	Key Findings	Comments
Camoriano et al, 1990[21]	391 premenopausal, node-positive cases; Mayo Clinic series	Mean, 6.6	Body weight and height at diagnosis	Increased risk of death with obesity for BMI ≥ 28 *v* BMI < 28 kg/m^2, *P* = .05; HR, 1.70; 95% CI, 0.99–2.94	
Coates et al, 1990[22]	1,960 pre- and postmenopausal cases ascertained at 14 hospitals in Georgia	> 5	Body weight and height at diagnosis	Significantly increased risk of death with obesity for BMI in the upper (≥ 24.6 kg/m^2) *v* lower (≤20.5 kg/m^2) tertiles; HR, 3.4; 95% CI, 2.3–4.8	Adjusted for stage, treatment, socioeconomic and menopausal status, prior cancer diagnosis, and family history of cancer
Kimura, 1990[26]	640 pre- and postmenopausal women undergoing radical partial mastectomy in Japan	10–16	Body weight and height at diagnosis	No significant differences were observed between three designated weight classes at 5 years; however, at 10 years, the survival rate among the lean group was 87.5%, among the ordinary group was 70.4%, and among the obese group was 68.8%, *P* < .05	Sample stratified by BMI as ≤ 21 kg/m^2 = lean, 21.1–23 kg/m^2 = ordinary, and > 23 kg/ m^2 = obese; data unadjusted
Kyogoku et al, 1990[27]	213 stage I-III cancers; pre- and postmenopausal cases ascertained at five hospitals in Japan	Mean, 10.2	Body weight and height within 3 months of surgery	Trend toward increased risk of mortality observed in crude analysis HR, 1.45 (*P* = .06) which became significant (*P* = .01) upon adjustment HR, 2.51 for BMI in the upper (≥ 25) *v* lower (< 20 kg/ m^2) quartiles.	Crude and adjusted (stage, treatment, age at menarche, age at first birth, menstrual status, smoking status, and history of abortion and benign breast disease) HR reported
Tretli et al, 1990[17]	8,427 pre- and postmenopausal cases within a national Norwegian study cohort	Mean, 4.3	Body weight and height obtained an average of 12.5 years before diagnosis	Significantly increased risk of death with obesity for stage I and II cancers (RR, 1.70; [95% CI, 1.29–2.25] and 1.42 [95% CI, 1.17–1.73], respectively, in the highest *v* lowest quintiles of BMI stratified by stage)	No relationship between obesity and survival for stage III and IV cancers
Vatten et al, 1991[18]	242 pre- and postmenopausal cases within a three-county Norwegian study cohort	Mean, 12	Body weight and height obtained an average of 8 years before diagnosis	Significantly increased risk of death with obesity for BMI in the highest (≥ 27) *v* lowest (< 22 kg/m^2) quartiles; unadjusted HR, 3.0 (95% CI, 1.3–6.7); adjusted HR, 2.1 (95% CI, 1.3–6.7)	Crude and adjusted (age, stage, and serum cholesterol concentration) HR reported
Gordon et al, 1992[23]	1,392 pre- and postmenopausal cases ascertained in the Midwest and Northeast United States	5–16	Body weight at diagnosis used in BMI calculation	Significantly decreased OS for BMI in the 95th *v* 5th percentile; unadjusted RR, 1.43; 95% CI, 1.09–1.88	No relationship between obesity and survival when analysis controlled for age, tumor ER status, and number of positive nodes
Senie et al, 1992[28]	923 pre- and postmenopausal cases; treated with mastectomy and axillary dissection; Memorial Sloan-Kettering series	10	Body weight and height at diagnosis	Significantly increased risk of death among obese (≥ 125% ideal body weight) *v* nonobese for overall sample and among node negative women (n = 557); total sample HR, 1.29 (95% CI, 1.00–1.67); node-negative HR, 1.59 (95% CI, 1.06–2.39	Adjusted for tumor size, number of positive nodes, age, and treatment with adjuvant chemotherapy
Tornberg and Carstensen, 1993[16]	1,170 pre- and postmenopausal cases within a national Swedish study cohort	Mean, 10	Premorbid weight	Significantly increased risk of death with obesity for BMI ≥ 28 *v* BMI < 22 kg/ m^2; HR, 1.70; 95% CI, 1.2–2.3	Adjusted for age
Bastarrachea et al, 1994[20]	735 pre- and postmenopausal cases; node-positive patients treated with adjuvant chemotherapy; M. D. Anderson series	Mean, 10.7	Body weight at diagnosis used to estimate relative weight	Significantly increased risk of recurrence and death, for obese (≥ 120% ideal body weight) *v* nonobese (RR, 1.36); risk of recurrence RR, 1.33 (95% CI, 1.05–1.68); risk of death RR, 1.36 (95% CI 1.06–1.76	Adjusted for menopausal status, stage, and number of positive axillary nodes
Jain and Miller, 1994[32]	174 pre- and postmenopausal invasive breast cancer cases within a national Canadian study cohort	Mean, 5.2	Body weight, height and triceps skinfold measures taken 7–12 years before diagnosis	No relationship observed between BMI and survival; significantly increased risk of death with higher *v* lower triceps skinfold; RR, 1.12; 95% CI, 1.01–1.24	Adjusted for age and number of positive axillary nodes; association with triceps skinfold adjusted for body weight

Study	Sample (size and key characteristics)	Years of Follow-Up	Time Point of Weight Status Indicator	Key Findings	Comments
Holmberg et al, 1994[14]	422 invasive breast cancer patients < 45 years old at diagnosis within a Swedish and Norwegian study cohort	5	Body weight and height self-reported at a mean of 18 months before diagnosis	Significantly increased risk of death for BMI ≥ 29 *v* < 19 kg/m^2; HR, 5.93 (95% CI, 1.98–17.80); when BMI analyzed as continuous variable, HR, 1.08 (95% CI 1.03–1.04) for every 8% increase in BMI	Adjusted for age and country of residence; continuous BMI analysis adjusted for age, parity, age at first birth, and education
Zhang et al, 1995[19]	698 cases with in situ to distant cancer cases within the Iowa Women's Health Study cohort	1–5 (median, 2.9)	Body weight and height self-reported within 6 years of diagnosis	Significantly increased risk of death with obesity when data age-adjusted (RR, 1.9; 95% CI, 1.0–3.7) for BMI in the upper (≥ 28.8) *v* lower (< 24.6 kg/m^2) tertiles; however, RRs become insignificant in multivariate analysis adjustment	Age-adjusted and multivariate-adjusted (age, smoking status, education, extent of cancer, and tumor size) RRs reported
den Tonkelaar et al, 1995[34]	241 pre- and postmenopausal cases within a national Netherlands study cohort	9.1	Body weight and height at initial screening and at diagnosis	No significant differences in mortality associated with obesity (BMI ≥ 26 *v* < 26 kg/m^2), based on BMI at screening or at diagnosis; RR, 1.91; 95% CI, 0.52–7.06	Increased risk for more advanced cancer among women with BMI ≥ 28 kg/m^2 (RR, 3.09; 95% CI, 1.28–7.51), but not translated into differences in mortality
Obermair et al, 1995[37]	473 pre- and postmenopausal primary cancer cases; University of Vienna series	6–126 months (mean, 61 months)	Body weight and height at diagnosis	No relationship with DFS for obese (> 25% above ideal body weight) *v* nonobese; RR, 0.83; 95% CI, 0.55–1.24	Adjusted for lymph node involvement, grade, tumor size, tumor ER and PgR status, and menopausal status
Lethaby et al, 1996[35]	1,138 pre- and postmenopausal node-negative cases within the Auckland cancer registry	Mean, 10.2	Body weight and height at diagnosis	No significant differences were observed in survival between women with BMI > 28 *v* those with BMI ≤ 28 kg/m^2; 10-year survival among younger cases was 74% *v* 67% in low *v* high BMI groups (P = .29), and 77% *v* 67%, respectively, among older cases (P = .13).	Log-rank tests unadjusted for other variables; separate analyses were performed for women < 50 years of age (n = 370) and women ≥ 50 years of age (n = 768)
Mæhle and Tretli, 1996[15]	1,238 pre- and postmenopausal cases; treated with modified radical mastectomy for unilateral cancer within a national Norwegian study cohort	Mean, 7.9	Body weight and height at a mean of 12.5 years before diagnosis	Crude analysis suggests significantly increased risk of death with obesity (highest versus lowest BMI quintiles) for total sample, as well as ER$^+$ patients (n = 215), but not in ER$^-$ patients (n = 215); however, with adjustment, the differences seen for the total and ER$^+$ patients were no longer observed; among the ER$^-$ sample a significantly inverse association was seen between body weight and mortality Total sample: crude RR, 1.49 (95% CI, 1.08–2.06), adjusted RR, 1.37 (95% CI, 0.99–1.90); ER$^+$ patients: crude RR, 2.36 (95% CI, 1.14–4.87), adjusted RR, 2.18 (95% CI, 1.05–4.53); ER$^-$ patients: crude RR, 0.49 (95% CI, 0.20–1.23), adjusted RR, 0.36 (95% CI, 0.14–0.90)	Crude and adjusted (tumor diameter, lymph node status, and nuclear area) RR reported
Haybittle et al, 1997[24]	2,455 pre- and postmenopausal cases with stage I or II cancers within a national United Kingdom cohort	5–20	Body weight at diagnosis	Significantly increased risk of death for > 60 versus ≤ 60 kg; RR, 1.68; 95% CI, 1.33–2.12	Adjusted for treatment
Jain and Miller, 1997[33]	275 pre- and postmenopausal cases within a national Canadian study cohort	Mean, 7.7	Body weight, height, and triceps skinfold measures obtained 7–12 years before diagnosis	No relationship between survival and obesity (based on BMI or skinfold); data reported for distinct subsets	Adjusted for age, smoking status, tumor hormone receptor status and size, and nodal status
Hebert et al, 1998[25]	472 pre- and postmenopausal patients with stage I-IIIA	8–10	Body weight and height at diagnosis	Incremental RR calculated for every 1 kg/m^2 increase; recurrence: total sample RR, 1.04 (95% CI, 1.00–1.09), premenopausal	Adjusted for age, stage, and consumption of meat, butter, and beer

Study	Sample (size and key characteristics)	Years of Follow-Up	Time Point of Weight Status Indicator	Key Findings	Comments
	cancers; Memorial Sloan-Kettering series			patients RR, 1.09 (95% CI, 1.02–1.17); mortality: total sample RR, 1.06 (95% CI, 1.00–1.12), premenopausal patients RR, 1.12 (95% CI, 1.03–1.22)	
Galanis et al, 1998[31]	365 pre- and postmenopausal cases within a statewide Hawaiian study cohort	Mean, 14.9	Body weight and height before diagnosis	Trend for increased risk of death with obesity for upper (BMI ≥ 25.8) *v* lower two (BMI < 22.6 kg/m^2) quintiles; RR, 2.2 (95% CI, 0.9–5.4)	Adjusted for age, stage, race, education, alcohol intake, and smoking status
Saxe et al, 1999[36]	149 pre- and postmenopausal cases with in situ to stage IV cancers; University of Michigan series	5–8	Body weight and height at diagnosis	No relationship between survival or recurrence and obesity (BMI > 27 *v* ≤ 27 kg/m^2)	Relationships examined both unadjusted and adjusted for tumor stage and other possible influencing variables
Kumar et al, 2000[38]	166 stage I-IV; pre- and postmenopausal, primary breast cancer patients not treated with either adjuvant chemotherapy or hormonal therapy and body weight ≤ 100 kg	≥ 10	Body weight, height, circumference, and skinfold measures obtained at diagnosis	Significantly reduced risk of death with obesity; significantly increased risk with higher *v* lower suprailiac:thigh ratio, which is an indicator of android obesity; HR for BMI, 0.92 (95% CI, 0.87–0.98); HR for increased suprailiac:thigh ratio, 2.6 (95% CI, 1.63–4.17)	Adjusted for stage
Daling et al, 2001[29]	1,177 patients < 45 years old at diagnosis with invasive ductal carcinoma identified through SEER registry in three Washington counties	7–17	Body weight and height 1 year before diagnosis	Significantly increased risk of death with obesity (HR 1.7 for highest [BMI ≥ 25.8] *v* lowest [BMI ≤ 20.6 kg/m^2] quartile); age-adjusted 5-year mortality HR, 2.5 (95% CI, 1.6–3.9); multivariate-adjusted 5-year mortality HR, 1.7 (95% CI, 1.0–2.9)	HR adjusted for age and diagnosis year, multivariate model adjusted for age, tumor size, lymph node status, tumor hormone receptor status, and tumor molecular characteristics
Marrett et al, 2001[39]	605 pre- and postmenopausal patients with invasive breast cancer < 4 cm diameter; treated with surgery, axillary dissection, and radiation therapy at a university hospital in Tours, France	Mean, 82 months	Body weight and height at diagnosis	Significantly reduced risk of local recurrence with obesity; HR, 0.92 (95% CI, 0.85–0.99) for every 1 kg/m^2 in BMI	Adjusted for age, positive axillary node status, and histologic multifocality
Goodwin et al, 2002[30]	512 pre- and postmenopausal patients with stage I-IIIA cancers without known diabetes diagnosed at three University of Toronto hospitals	Median, 50 months	Body weight and height within 3 months of surgery	Linear log hazard models suggest a significant positive association between BMI and distant DFS (P = .047), but not OS (P = .063); however, when nonlinear models were used, there was a significant relationship (P < .001) for both distant DFS and OS, with worse outcomes occurring in women whose BMIs were < 20 or > 25 kg/m^2	Adjusted for age, stage, receptor status, and adjuvant chemotherapy and tamoxifen

Abbreviations: BMI, body mass index (weight [kg]/height [m^2]); CI, confidence interval; ER, estrogen receptor; PgR, progesterone receptor; HR, hazard ratio; RR, relative risk; SEER, Surveillance, Epidemiology and End Results Program of the National Cancer Institute; DFS, disease-free survival; OS, overall survival.

Table 2

Prospective Studies of Diet, Survival, and Recurrence After Breast Cancer Diagnosis

Study	Sample (size and key characteristics)	Years of Follow-Up	Dietary Assessment Methodology	Dietary Variables Analyzed	Key Findings	Comments
Gregorio et al, 1985[79]	953 patients aged ≥ 46 years with local-distant cancers; Roswell Park series	18–26	Interview to obtain usual frequency of consuming 33 foods and beverages in the year before diagnosis	Total fat intake	Significantly increased risk of death with increased fat intake in women with regional and distant disease; RR, 1.44 for each 1,000 g/mo fat intake for distant disease ($P < .01$)	Controlled for disease stage and age at diagnosis; fat intake not energy adjusted; relationship not significant in women with local disease
Newman et al, 1986[80]	300 patients aged 35–74 years with nonmetastatic cancers identified in four cities in Canada	5–7	Combined data from interview, recall, and record to assess intake during a 2-month period 1–5 months after surgery	Total fat intake	No relationship between fat intake and risk of death	Controlled for relative body weight; fat intake not energy adjusted
Nomura et al, 1991[81]	182 Japanese and 161 white patients aged 45–74 years with in situ to distant cancers identified at seven hospitals in Oahu, HI	7–12	Interview to obtain usual intake of 43 foods, plus recall for usual intake at an average of 2.2 months after diagnosis	Total fat intake	Significantly increased risk of death with increased fat intake in white subgroup; RR, 3.17 (95% CI, 1.17–8.55) for high *v* low intakes	Adjusted for disease stage, menopausal status, obesity index, and estrogen use; fat intake not energy adjusted
Ewertz et al, 1991[82]	2,445 patients < 70 years of age with stage I-III cancers identified through the Danish Breast Cancer Cooperative Group and Danish Cancer Registry	6–7	Self-administered food frequency questionnaire at 1 year after diagnosis	Total fat and alcohol intake; meat and vegetables (data not shown for the latter items)	No relationship between total fat or meat intake and risk of death; risk of dying "slightly decreased for frequent consumption of vegetables and increased for alcohol consumption," but not significant	Adjusted for age and disease stage; fat intake not energy adjusted
Kyogoku et al, 1992[83]	212 patients (average age, 55.5 years) with stage I-III cancers ascertained at five hospitals in Japan	9–12	Interview to obtain frequency and amounts of foods consumed in a typical week before disease onset	Total fat; animal, fish, and vegetable fat; animal protein intake	No relationship between fat intake and risk of death	Adjusted for stage, BMI, age at menarche, age at first birth, treatment modality, and each of the nutrients (none were energy adjusted)
Holm et al, 1993[84]	240 patients with stage I and II cancers (13% pre- and 87% postmenopausal) identified in the Stockholm region of Sweden	4	Detailed diet history interview within 4 months of diagnosis to ascertain intake during the past year	Energy, alcohol, and nutrient intakes	In χ^2 analysis, significantly increased risk of "treatment failure" (recurrence or new cancer in contralateral breast) with increased total fat and saturated fat intake (energy-adjusted) in women with ER^+ tumors; OR, 1.13 for fat (95% CI, 1.03–1.45); OR, 1.23 for saturated fat (95% CI, 1.05–1.45), for each percent energy increase	No relationship between intake and risk in women with ER negative status; no significant relationships with disease-free survival when adjusted for stage in Cox analysis

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Study	Sample (size and key characteristics)	Years of Follow-Up	Dietary Assessment Methodology	Dietary Variables Analyzed	Key Findings	Comments
Rohan et al, 1993[85]	412 patients aged 20–74 years at diagnosis identified through the South Australian Central Cancer Registry	0.5–7.4 (median, 5.5)	Self-administered food frequency questionnaire completed within 4.8 months after diagnosis	Energy, alcohol, and nutrient intakes	Point estimates suggest associations between increased risk of death with increased fat intake and decreased beta-carotene and vitamin C intakes; fat HR, 1.40 (95% CI, 0.66–2.96); beta-carotene HR, 0.78 (95% CI, 0.36–1.27); vitamin C HR, 0.76 (95% CI, 0.42–1.30) for highest *v* lowest quintile	Adjusted for energy intake, age at menarche, and BMI
Ingram, 1994[86]	103 pre- and postmenopausal cases ascertained at a medical center in Perth, Australia	6	Self-administered food frequency questionnaire 3 months after surgery, focused on intake before diagnosis	Energy, alcohol, and nutrient intakes and food groups at diagnosis	Significantly decreased risk of death in women in highest tertile of beta-carotene, vitamin C, fruit, and vegetable and fruit intakes; observed/expected deaths for highest tertile of intake were 0.10 for beta-carotene, 0.40 for vitamin C, and 0.60 for vegetables and fruit (P = .001, .03, and .04, respectively)	Not adjusted for stage of disease
Jain et al, 1994[78]	678 patients aged 45–64 years within the Canadian National Breast Screening Study cohort	7–12 (5-year survival reported)	Self-administered food frequency questionnaire completed before diagnosis, focused on previous month's intake	Energy, alcohol, and nutrient intakes at diagnosis	Significantly increased risk of death with increased energy-adjusted saturated fat intake (HR, 1.44; 95% CI, 1.16–1.78); significantly lower risk of death with increased beta-carotene (HR, 0.80; 95% CI, 0.65–0.99) and vitamin C (HR, 0.77; 95% CI, 0.62–0.95) intakes	No significant increase in risk associated with total fat intake; adjusted for age, smoking, and body weight
Zhang et al, 1995[19]	698 patients aged 56–67 years with in situ to distant cancers within the Iowa Women's Health Study cohort	1–5 (median, 2.9)	Self-administered food frequency questionnaire	Energy, alcohol, and nutrient intakes at diagnosis	Significantly increased risk of death with increased total fat (RR, 2.1; 95% CI, 1.1–4.3) and polyunsaturated fat (RR, 2.0; 95% CI, 1.0–3.8) intakes, for higher *v* lowest tertiles	Adjusted for age; no significant relationships with fat when energy adjusted
Hebert et al, 1998[25]	472 patients aged 20–70 years with stage I-IIIA cancers; Memorial Sloan-Kettering series	8–10	Food frequency questionnaire completed at the time of diagnosis and 2 years thereafter	Selected food groups	Significantly increased risk of recurrence with energy-adjusted butter, margarine, and lard (RR, 1.30 and 95% CI, 1.03–1.64 for each time/d consumed) and beer (RR, 1.41 and 95% CI, 1.02–1.97 for each drink/d) intakes	Adjusted for age, stage, BMI, menopausal status, and other foods; no significant associations with wine or liquor; relationships not significant for risk of death

Study	Sample (size and key characteristics)	Years of Follow-Up	Dietary Assessment Methodology	Dietary Variables Analyzed	Key Findings	Comments
Saxe et al, 1999[36]	149 patients aged 26–95 years with in situ stage IV cancers; University of Michigan series	5–8	Self-administered food frequency questionnaire completed at the time of diagnosis or at the first postoperative clinic visit, focused on intake during the year before diagnosis	Energy, alcohol, and nutrient intakes at diagnosis	Significantly increased risk of death with energy intake (HR, 1.58 and 95% CI, 1.03–2.43 per 1,000 kcal/d); increased risk of recurrence with increased energy intake (HR, 1.84 and 95% CI, 1.19–2.86 per 1,000 kcal/d) and decreased risk with increased energy-adjusted bread and cereal intake (HR, 0.63 and 95% CI, 0.38–1.04 per seven servings/ wk)	Adjusted for tumor stage, oral contraceptive use, and BMI
Holmes et al, 1999[87]	1,982 patients (mean age, 54 years) with invasive breast cancer within the Nurses' Health Study cohort	4–18 (mean, 13)	Self-administered food frequency questionnaire completed > 12 months after diagnosis	Energy, alcohol, and nutrient intakes after diagnosis	Significantly reduced risk of death with increased protein intake (RR, 0.65 and 95% CI, 0.47–0.88 for highest *v* lowest quintile); protective effects of vegetable, fiber, and omega-3 fatty acid intakes (RR, 0.62 [95% CI, 0.36–1.07], 0.59 [95% CI, 0.33–1.08], and 0.52 [95% CI, 0.30–0.93], respectively, in highest *v* lowest quintile) in women with node-negative disease (n = 1,237)	Controlled for age, BMI, oral contraceptive use, menopausal status, postmenopausal hormone use, smoking, age at first birth, parity, tumor size, and energy intake

Abbreviation: OR, odds ratio.