VOLUME 28 · NUMBER 26 · SEPTEMBER 10 2010

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Weight, Physical Activity, Diet, and Prognosis in Breast and Gynecologic Cancers

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Submitted January 4, 2010; accepted May 25, 2010; published online ahead of print at www.jco.org on July 19, 2010.

Supported by Grants No. NO1-PC-55020-20, U54-CA116847, and R01 CA105204 from the National Cancer Institute.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/10/2826-4074/$20.00

DOI: 10.1200/JCO.2010.27.9752

ABSTRACT

Diet, physical activity, and weight may affect prognosis among women who are diagnosed with breast or gynecologic cancer. Observational studies show associations between being overweight or obese and weight gain with several measures of reduced prognosis in women with breast cancer and some suggestion of poor prognosis in underweight women. Observational studies have shown an association between higher levels of physical activity and improved breast cancer–specific and all-cause mortality, although a dose-response relationship has not been established. One large randomized controlled trial reported increased disease-free survival after a mean of 5 years in patients with breast cancer randomly assigned to a low-fat diet versus control. However, another trial of similar size found no effect from a high vegetable/fruit, low-fat diet on breast cancer prognosis. The few reported studies suggest that obesity negatively affects endometrial cancer survival, while the limited data are mixed for associations of weight with ovarian cancer prognosis. Insufficient data exist for assessing associations of weight, physical activity, or diet with prognosis in other gynecologic cancers. Associations of particular micronutrient intake and alcohol use with prognosis are not defined for any of these cancers. The effects of dietary weight loss and increase in physical activity on survival or recurrence in breast and gynecologic cancers are not yet established, and randomized controlled trials are needed for definitive data.

J Clin Oncol 28:4074-4080. © 2010 by American Society of Clinical Oncology

INTRODUCTION

In 2006, the American Cancer Society recommended[1] that patients with cancer maintain normal weight, increase physical activity, and eat a diet low in fat and refined carbohydrates and high in vegetables and fruits, as a potential aid to some aspects of prognosis, acknowledging the lack of definitive data. If lifestyle factors could be confirmed as important in cancer prognosis, they may provide additional options for cancer survivors to maximize health and well-being.

This article reviews the literature on associations between weight, physical activity, dietary patterns, specific nutrients, and prognosis variables (ie, cancer specific mortality, all-cause mortality, recurrence, and second primary cancers) in breast, ovarian, and endometrial cancers in women. Other gynecologic cancers (eg, cervical, vagina, vulva) have not been studied in relation to these lifestyle factors and prognosis, and therefore are not included. Studies considered for this review were obtained from PubMed searches on the search terms breast, ovary, endometrium, cancer, obesity, weight gain, weight loss, exercise, physical activity, diet, prognosis, and survival. We referenced comprehensive reviews of obesity, diet, and breast cancer prognosis that were published in 2002.[2,3] Therefore, for these specific sections, we only searched for studies published after 2002.

Many observational studies and a few randomized clinical trials have investigated the associations of diet, physical activity, or weight with prognosis among women diagnosed with breast or gynecologic cancer, as we discuss in the following sections. Table 1 summarizes our findings graphically.

WEIGHT AND BODY COMPOSITION

Being overweight, obese, or underweight may increase risk of breast and gynecologic cancer recurrence or death, although the effect of weight change on prognosis has not been established. Being overweight or obese may also increase the risk of several complications from cancer treatment and increase the risk of several comorbidities.

BREAST

A 1992 meta-analysis estimated that being overweight (body mass index [BMI], 25.0 to 29.9 kg/m^2)

Table 1. Obesity, Physical Activity, and Diet Associations With Breast, Ovarian, and Endometrial Cancer Overall or Cancer-Specific Survival

Lifestyle Factor	Survival		
	Breast	Ovary*	Endometrium*
Obesity/overweight	↓ ↓ †	⇆	↓
Underweight	↓	?	?
Weight gain	?	↑	?
Weight loss	↓ ‡	↓	?
Physical activity	↑	?	?
Dietary pattern (low fat, increased fruit/vegetables)	⇆	?	?
Alcohol	↑	?	?

*Evidence based on one to two studies in each lifestyle factor.
†Double symbol indicates strong evidence, with most published studies indicating associations between obesity and poorer survival.
‡Few cohort studies of weight loss and survival, but Women's Intervention Nutrition Study result with 6 lb intervention versus control difference at median 60 months follow-up suggests weight loss could be associated with improved survival.

or obese (BMI $\geq$ 30 kg/m^2) was associated with a statistically significantly 78% to 91% increased risk of recurrence, and a 36% to 56% increased risk of death in women with breast cancer.[4] A 2002 comprehensive review concluded that a statistically significant association between being overweight or obese and increased recurrence or mortality was seen in 26 of 40 studies including 29,460 women with breast cancer, while several studies with more than 5,000 women did not see such associations.[2] Subsequently, several large cohort studies have investigated the associations between being overweight/obese and breast cancer prognosis. Most have found an association between higher weight or BMI with reduced survival or increased recurrence,[5-11] although not all studies support this.[12] Negative associations between excess body weight and breast cancer recurrence and survival have been observed in both pre- and postmenopausal women.[2]

A few studies have assessed the association of underweight (typically BMI $<$ 18.5 kg/m^2) with breast cancer prognosis, and found that, compared with normal weight women (BMI, 18.5 to 25.0), underweight women have reduced overall and breast cancer–specific survival.[7,13,14]

Several studies have investigated interactions between being overweight/obese and adjuvant therapy effectiveness. A National Surgical Adjuvant Breast and Bowel Project analysis of 3,385 clinical trial patients from a randomized, placebo-controlled trial evaluating tamoxifen for lymph node–negative, estrogen receptor–positive breast cancer found that obese women benefited from tamoxifen therapy as much as lighter-weight women.[8] Compared with normal-weight women, however, obese women had greater all-cause mortality (hazard ratio [HR], 1.31; 95% CI, 1.12 to 1.54) and nonbreast cancer mortality (HR, 1.49; 95% CI, 1.15 to 1.92).

Two studies have reported on body fat distribution in relation to breast cancer prognosis, with suggestions of increased breast cancer mortality risk with android body fat distribution defined as high waist-to-hip ratio,[15] or as high suprailiac-to-thigh ratio.[16]

Risk of future second primary breast cancer may also be increased with higher levels of adiposity. Results from a population-based cohort of 1,285 breast cancer survivors suggest an increased risk for contralateral breast cancer among overweight or obese breast cancer survivors.[17] In the National Surgical Adjuvant Breast and Bowel Project analysis of 3,385 tamoxifen trial patients, risk for contralateral breast cancer was increased in obese versus underweight/normal-weight women (HR, 1.58; 95% CI, 1.10 to 2.25), as was the risk of additional primary breast cancers (HR, 1.62; 95% CI, 1.16 to 2.24).[8]

ENDOMETRIUM

Up to 90% of women with type 1 endometrial cancer, the most common type, are overweight or obese.[18] In an analysis of 380 early-stage endometrial cancer patients from a randomized trial of surgery with or without adjuvant radiation therapy, mortality was increased in patients with BMI 30 to 39.9 (HR, 1.48; 95% CI, 0.82 to 2.70; $P = .196$) and in patients with BMI $\geq$ 40 kg/m^2 (HR, 2.77; 95% CI, 1.21 to 6.36; $P = .016$), compared with lighter-weight women.[19] In an analysis of patients with advanced or recurrent endometrial cancer from five Gynecology Oncology Group trials who had been treated with adjuvant chemotherapy of doxorubicin and cisplatin, no overall significant associations between progression-free survival and BMI were detected.[20] However, increased BMI was significantly associated with an increased risk of death in women with stage III/IV endometrial cancer (HR, 1.86; 95% CI, 1.16 to 2.99 for BMI $\geq$ 40 kg/m^2 *v* BMI $<$ 25 kg/m^2), but not in patients with recurrent disease.

OVARY

Approximately 30% of patients with ovarian cancer are overweight and 12% are obese.[21] Some studies have indicated that obesity is a negative prognostic indicator for survival while others did not show a demonstrable difference in overall outcomes.[21-25] In a retrospective hospital-based study in 200 patients with advanced-stage disease, obesity was independently associated with shorter disease-free ($P = .02$) and overall survival ($P = .02$), although information on chemotherapy and debulking status was incomplete.[22] In a study of more than 300 patients who underwent primary cytoreductive surgery followed by taxane/platinum-based chemotherapy, survival rates were similar between obese and nonobese patients when optimal debulking status was identical.[23] However, this study had incomplete chemotherapy data, and therefore confounding by treatment cannot be ruled out.

Inconsistencies in dosing chemotherapy for obese patients have included use of body surface area, dosing at ideal body weight, dose capping, and differing measurements of renal function, all of which can underestimate dose and consequently negatively influence survival.[21,24] In the Scottish Randomized Trial in Ovarian Cancer I trial, in which more than 1,000 patients received first-line taxane/carboplatin chemotherapy, BMI was not associated with progression-free survival, overall survival, tumor stage or grade at presentation, or completeness of debulking surgery.[21]

WEIGHT CHANGE AFTER DIAGNOSIS AND RISK OF MORTALITY

Breast

Weight gain after diagnosis has been frequently reported for patients with breast cancer, especially among women receiving systemic adjuvant chemotherapy[2,26]; with weight gains between 2 and 4 kg after some chemotherapy regimens such as cyclophosphamide,

methotrexate, and fluorouracil.[27,28] Tamoxifen treatment does not appear to influence body weight,[26] and the effect of aromatase inhibitors on weight is not established. At least eight studies have investigated the relationship between weight gain after diagnosis and prognosis,[26,29-35] of which three reported increased recurrence risk or decreased survival with weight gain.[30,31,35] One population-based cohort study suggested that weight loss from pre- to postdiagnosis may increase risk of mortality in women with breast cancer.[12]

Endometrium and Ovary

Although some patients with endometrial cancer gain weight after diagnosis, the effect of this weight gain on recurrence or mortality is unknown.[19]

In an analysis of 792 advanced patients with ovarian cancer, no association between prechemotherapy BMI and survival was observed.[25] Weight gain was associated with improved survival, however: median overall survival was 48.0, 49.3, 61.1, and 68.2 months, respectively, for weight changes of more than 5% decrease, 0% to 5% decrease, 0% to 5% increase, and more than 5% increase during chemotherapy. The relative risk of death increased by 7% for each 5% decrease in body weight (HR, 0.93; 95% CI, 0.88 to 0.99; $P = .013$).

OBESITY AND DEVELOPMENT OF COMORBIDITIES IN PATIENTS WITH CANCER

Obese patients with cancer are at increased risk for morbidities including surgical wound complications, lymphedema, and possibly, congestive heart failure if treated with doxorubicin.[36] Obesity also may increase risk for development of endometrial cancer among women with breast cancer treated with tamoxifen.[37] Obesity increases risk of several cancers in addition to breast and endometrium, including kidney, esophageal adenocarcinoma, and colon.[38] Finally, overweight or obese cancer survivors may suffer from obesity-related comorbidities including type II diabetes, hypertension, cardiovascular disease, osteoarthritis, and pulmonary disease.[39,40]

Physical Activity and Cancer Prognosis: Breast, Endometrium, and Ovary

Recent publications have reported on associations between physical activity after diagnosis and prognosis among breast cancer survivors. In 2,987 women from the Nurses' Health Study diagnosed with stage I to III breast cancer between 1984 and 1998 and followed until death or 2002, the relative risk of death from breast cancer for activity equivalents of walking was 0.80 for 1 to 3 hours/wk; 0.50 for 3 to 5 hours/wk; 0.56 for 5 to 8 hours/wk; and 0.60 for $\geq$ 8 hours/wk, compared with inactive women.[41] In a cohort of 688 women diagnosed with local or regional breast cancer (the Health, Eating, and Lifestyle [HEAL] study) between 1995 and 1998 and observed until death or 2004, the HR for total deaths for women expending the energy equivalent of 2 to 3 hours/wk of brisk walking at 2 years after diagnosis was 0.33 (95% CI, 0.15 to 0.73, P for trend = .046) compared with inactive women.[42] In a cohort of 1,970 early-stage patients with breast cancer identified primarily through a health maintenance organization, a protective association between physical activity and all-cause mortality remained in multivariable analyses (HR, 0.66; 95% CI, 0.42 to 1.03; P for trend = .04).[43] An analysis of lifestyle and survival in the control arm of the Women's Healthy Eating and Living Study (WHEL) trial found that the combination of consuming five or more daily servings of vegetables and fruits, and accumulating $\geq$ 540 metabolic equivalent tasks-minutes/wk (equivalent to walking 30 minutes 6 days/wk), was associated with a significant survival advantage (HR, 0.56; 95% CI, 0.31 to 0.98).[44] The findings were similar in obese and nonobese women, and were strongest in those with estrogen receptor–positive tumors. In a cohort of 4,482 women with early-stage breast cancer followed for approximately 6 years, compared with women expending less than 2.8 MET-hours/wk in physical activity, women who engaged in more than 2.8 MET-hours/wk had a significantly lower risk of dying from breast cancer (HR, 0.65; 95% CI, 0.39 to 1.08 for 2.8 to 7.9 MET-h/wk; HR, 0.59; 95% CI, 0.35 to 1.01 for 8.0 to 20.9 MET-h/wk; and HR, 0.51; 95% CI, 0.29 to 0.89 for $\geq$ 21.0 MET-h/wk; P for trend = .05). Results were similar for overall survival, and were similar regardless of age, stage of disease, and BMI.[45]

There are no published studies on the associations between physical activity and endometrial or ovarian cancer prognosis.

Dietary Composition and Cancer Prognosis

Breast. In the Women's Intervention Nutrition Study (WINS), 2,437 women with breast cancer were randomly assigned between 1994 and 2001 in a ratio of 40:60 to a low-fat dietary intervention (n = 975) or control (n = 1462) groups and followed for a median 60 months (Table 2).[46] A total of 277 relapse events (local, regional, distant, or ipsilateral breast cancer recurrence or new contralateral breast cancer) were reported in 96 (9.8%) of 975 women in the dietary group and 181 (12.4%) of 1,462 women in the control group. The HR of relapse events in the intervention group compared with the control group was 0.76 (95% CI, 0.60 to 0.98, $P = .077$ for stratified log-rank and $P = .034$ for adjusted Cox model analysis). Exploratory analyses suggested a greater effect of the dietary intervention among women with hormone receptor negative tumors. WHEL was a randomized clinical trial of high fruit and vegetable and low-fat diet versus usual diet in 3,088 early-stage breast cancer survivors. Despite high intervention adherence, rates of second breast cancer with 7.3 years follow-up were similar in the two arms of this trial (HR, 0.96; 95% CI, 0.80 to 1.14) and mortality was lower, but not significantly so in the diet intervention arm (HR, 0.91; 95% CI, 0.72 to 1.15).[47] While weight loss was not a specific intervention target in the WINS trial, significantly lower body weight was seen in the intervention group throughout (6 pound mean difference at median 60 months follow-up). This could be one explanation for the discrepant findings between WINS and WHEL, because the latter intervention did not result in weight loss.

A review of observational cohort studies from 1985 to 2002 concluded that five of eight cohort studies of breast cancer survivors that examined intakes of vegetables, fruit, and related micronutrients reported a positive relationship between these factors and survival.[3] A recent study of 1,901 early-stage patients with breast cancer indicated that women following a diet with high intakes of fruits, vegetables, whole grains, and poultry had statistically significant decreasing risk of overall death (P trend = .02; HR for highest quartile, 0.57; 95% CI, 0.36 to 0.90) and death from nonbreast cancer causes (P trend = .003; HR for highest quartile, 0.35; 95% CI, 0.17 to 0.73).[48]

While alcohol use increases risk for breast cancer,[49] studies are not consistent regarding the association of alcohol use with breast cancer events. Early studies found that alcohol use after diagnosis is

Table 2. Comparison of WINS[46] and WHEL[47] Trials: Designs, Interventions, and Findings

Parameter	WINS Mean	WINS SD	WHEL Mean	WHEL SD
Eligibility				
Stage	I-III A		I-III A	
Time from surgery, months	≤ 12		≤ 48	
Chemotherapy	AC, CMF, FAC, or AC → paclitaxel		Any (before randomization)	
Hormone therapy	Tamoxifen		Any	
Receptor status	Any		Any	
Age, years	48-79		18-70	
Weight/body mass index	Any		Any	
Diet at baseline	≥ 20% calories from fat		Any	
Dietary intervention				
Intervention phase	Eight individual dietitian visits over 16 weeks		18 telephone calls over 12 months, four cooking classes (average attended)	
Maintenance phase	Individual dietitian visits every 3 months		Telephone calls every 3 months	
No. of patients	2,437		3,088	
Random assignment type	3:2		1:1	
Intervention target				
Fat	↓ to 15% calories from fat		↓ to < 20% calories from fat	
Calories	No target			
Vegetable	↑ (no target)		↑ to 5 serving/day and 16 oz vegetable juice/day	
Fruit	↑ (no target)		Increase to three servings/day	
Body weight	NA		NA	
Physical activity	NA		NA	
Follow-up interval, years	5		7.3	
End point	Relapse-free survival		Breast cancer event-free survival	
Self monitoring	Daily keeping score book		No	
Dietary assessment	Two 24-hour unannounced telephone calls/year		Four prescheduled 24-hour telephone calls at 1, 4, and 6 years	
End point events, No.	277		518	
Primary breast cancer outcome	HR, 0.76; 95% CI, 0.60 to 0.98; $P = .034$		HR, 0.96; 95% CI, 0.80 to 1.14; $P = .63$	
% energy from fat				
Baseline	29.6	7.1	28.5	0.18
1 year	20.3	7.8	22.7	0.20
4 year	22.6	8.5	27.1	0.24
6 year	23.0	9.2	28.9	0.25
Body weight, kg				
Baseline	72.7	15.9	73.5	0.42
1 year	70.6	15.2	73.0	0.45
4 year	71.2	14.9	74.2	0.51
6 year	69.4	13.9	74.1	0.54
Fiber g/day				
Baseline	18.4	4.1	21.1	0.21
1 year	19.5	4.7	29.0	0.28
Vegetable servings/day				
Baseline	Not reported		3.9	0.06
1 year	—		7.8	0.09
Fruit servings/day				
Baseline	Not reported		3.5	0.05
1 year	—		4.2	0.06

Abbreviations: WINS, Women's Intervention Nutrition Study; WHEL, Women's Healthy Eating and Living Study; SD, standard deviation; AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and fluorouracil; FAC, fluorouracil, doxorubicin, and cyclophosphamide; NA, not available; HR, hazard ratio.

associated with lower risk of recurrence or death,[3,7] while a recent study found a two-fold increased risk for second primary breast cancers in women who drank at least 7 alcohol drinks/wk compared with nondrinkers.[50]

Endometrium and ovary. There are no published studies of diet and endometrial cancer survival.

There are few data on diet and prognosis in patients with ovarian cancer. In a population-based cohort of 609 women with epithelial

ovarian cancer observed for up to 5 years, the HR for death was reduced in women who reported higher intake of vegetables before diagnosis (HR, 0.75; 95% CI, 0.57 to 0.99; $P = .01$), and cruciferous vegetables (HR, 0.75; 95% CI, 0.57 to 0.98; $P = .03$).[51] Inverse associations were seen with protein ($P = .09$), red meat ($P = .06$), and white meat ($P = .07$) with survival.

POTENTIAL MECHANISMS FOR EFFECTS OF OBESITY, DIET AND PHYSICAL ACTIVITY ON BREAST CANCER PROGNOSIS

Several mechanisms have been proposed for a prognostic effect of obesity, diet, and physical activity in cancer.[2,52] These mechanisms include circulating or tissue levels of sex and metabolic hormones; levels of hormone binding proteins; levels of inflammation and other cytokines; and chemotherapy underdosing in obese patients.

Excess estrogens and androgens are related to reduced prognosis as supported by some[53,54] but not all observational data,[13] and by the effect of antiestrogens or withdrawal of endogenous estrogens as adjuvant treatments for breast cancer.[55] Overweight and obese patients with breast cancer and survivors have elevated blood levels of estrogens and androgens,[56] and a high fiber, high vegetable/fruit, low-fat diet intervention may lower sex hormone levels in women with a history of breast cancer.[57]

Levels of insulin and C-peptide are elevated in overweight/obese and sedentary individuals and are reduced with either weight loss or regular exercise.[58] In a study of 535 women with early-stage breast cancer, women in the highest quartile of fasting insulin levels had a 2.1 times increased risk of distant recurrence compared to those in the lowest quartile (95% CI, 1.2 to 3.6; $P = .01$) and a 3.3 times greater risk of death (95% CI, 1.5 to 7.0; $P = .002$; adjusted for age, nodal stage, tumor stage, tumor grade, hormone receptor status, adjuvant chemotherapy, adjuvant tamoxifen).[13] The effect of insulin on survival was independent of BMI. In a cohort of 571 breast cancer survivors diagnosed with stage I to IIIa breast cancer and observed for 5 to 8 years (median, 6 years), fasting C-peptide levels at approximately 3 years postdiagnosis among women without type 2 diabetes were associated with an increased risk of death as a result of all causes or breast cancer. [59]A 1-ng/mL increase in C-peptide was associated with a 34% increased risk of death (HR, 1.34; 95% CI, 1.07 to 1.69; $P = .013$) and a 58% increased risk of breast cancer death (HR, 1.58; 95% CI, 1.15 to 2.16; $P = .0048$) after adjustment for confounding variables. Women with C-peptide levels higher than 2.5 ng/mL had an approximate four-fold increased risk of breast cancer death compared with women with a C-peptide level lower than 1.7 ng/mL (HR, 3.90; 95% CI, 1.16 to 13.13; P for trend $= .028$). Another report from this study found that decreased adiponectin levels and greater insulin resistance were associated with decreased breast cancer deaths and with all-cause mortality.[60]

Two small clinical trials have demonstrated that 4 to 6 months of aerobic exercise interventions with or without resistance training in breast cancer survivors produces significant reductions in obesity related hormones including insulin and insulin-like growth factor.[61,62]

Being overweight, obese, and lack of physical activity are associated with elevated inflammatory markers including C-reactive protein, serum amyloid A, interleukin-6, interleukin-1, and tumor necrosis factor-α, some of which been shown to be higher in patients with metastatic cancer compared with healthy persons and with persons with early-stage cancer.[2,63] In 731 patients with breast cancer diagnosed with early-stage breast cancer, the inflammation markers C-reactive protein and serum amyloid A if elevated when measured at approximately 31 months postdiagnosis were associated with reduced overall survival (P trend $< .002$ and $< .0001$, respectively).[64] The hazard ratios for C-reactive protein and serum amyloid A tertiles suggested a threshold effect on death, rather than a dose-response relationship (HRs for highest *v* lowest tertile: 2.27 and 3.15, respectively). Elevated C-reactive protein and serum amyloid A were also marginally associated with reduced disease-free survival.

SUMMARY

Observational data show strong evidence that increased adiposity and a sedentary lifestyle are associated with decreased prognosis in women with breast cancer, and a suggestion of reduced prognosis with being underweight. Data are much more limited for endometrial and ovarian cancers, but small studies suggest some effect of either obesity or being underweight and decreased prognosis for these cancers. The worldwide trends of increased numbers of overweight and obese individuals and decreased physical activity may lead to an increasing incidence of breast and gynecologic cancers unless other means of risk reduction counteract these effects. This will result in a larger proportion of women with these cancers being overweight, obese, and sedentary, thus the clinical implications are significant. There are no firm data linking specific dietary macronutrient or micronutrients with prognosis in any of these cancers, although one randomized trial found that women assigned to a low-fat dietary pattern that included some long-term weight changes had improved prognosis compared with controls.

There have been no randomized clinical trials testing the effect of weight loss or physical activity interventions on recurrence or survival in overweight or obese patients with breast or gynecologic cancer. In the absence of clinical trial data, most individual patients should be advised to avoid weight gain throughout the cancer treatment process. In addition, weight loss through dietary change is probably safe, and perhaps helpful, for overweight and obese breast and gynecologic cancer survivors who are otherwise healthy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Anne McTiernan
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