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Cancer Epidemiology, Biomarkers & Prevention

Review

The Role of Obesity in Cancer Survival and Recurrence

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Abstract

Obesity and components of energy imbalance, that is, excessive energy intake and suboptimal levels of physical activity, are established risk factors for cancer incidence. Accumulating evidence suggests that these factors also may be important after the diagnosis of cancer and influence the course of disease, as well as overall health, well-being, and survival. Lifestyle and medical interventions that effectively modify these factors could potentially be harnessed as a means of cancer control. However, for such interventions to be maximally effective and sustainable, broad sweeping scientific discoveries ranging from molecular and cellular advances, to developments in delivering interventions on both individual and societal levels are needed. This review summarizes key discussion topics that were addressed in a recent Institute of Medicine Workshop entitled, "The Role of Obesity in Cancer Survival and Recurrence"; discussions included (i) mechanisms associated with obesity and energy balance that influence cancer progression; (ii) complexities of studying and interpreting energy balance in relation to cancer recurrence and survival; (iii) associations between obesity and cancer risk, recurrence, and mortality; (iv) interventions that promote weight loss, increased physical activity, and negative energy balance as a means of cancer control; and (v) future directions. *Cancer Epidemiol Biomarkers Prev; 21(8); 1244–59. ©2012 AACR.*

Introduction

The hazards of obesity were first noted by the ancient Greeks. Hippocrates (460–370 BC), the "Father of Medicine" and the first to characterize the crab-like structure of cancer that he termed "karkinos," warned of the dangers of too much food and too little exercise (1). Almost 2 millennia later, Robert Thomas chronicled the link between obesity and endometrial cancer (2). Discoveries over the past century have significantly improved our understanding of the interrelationships between overweight/obesity, energy balance and cancer risk, as well as cancer recurrence and survival (2). Consensus now exists that obesity is a risk factor for cancers of the endometrium, colorectum, kidney, esophagus, breast (postmenopause), and pancreas, and evidence continues to mount about associations with cancers of the thyroid, gallbladder, liver, ovary, and aggressive forms of prostate cancer, as well as non-Hodgkin lymphoma (3, 4). Moreover, obesity is increasingly recognized as a poor prognostic factor for several common malignancies (5–8). The effects of obesity on cancer incidence and poor outcomes in patients with cancer are especially worrisome in light of the obesity epidemic (9). Worldwide, estimates indicate that 1.5 billion adults are overweight [body mass index (BMI): 25–29.9 kg/m^2] and 500 million are obese (BMI $\geq$ 30 kg/m^2; ref. 10). Also, with the earlier onset of overweight and obesity often occurring during childhood, there is considerable concern, as the life-time effects of obesity on cancer outcomes are yet unknown.

In a recent workshop convened by the Institute of Medicine's (IOM) National Cancer Policy Forum (October 31–Nov 1, 2011), experts in the fields of cancer survivorship and obesity met to discuss converging trends and the research gaps that exist (11). Discussions included (i) mechanisms associated with obesity and energy balance that influence cancer progression; (ii) complexities of studying and interpreting energy balance in relation to cancer recurrence and survival; (iii) associations between

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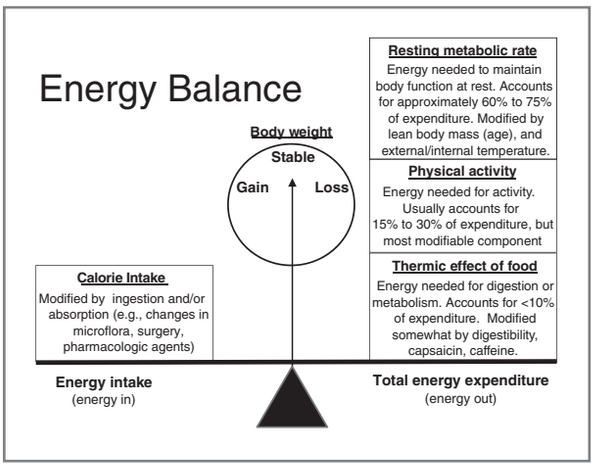

Figure 1. The complex dynamic nature of energy balance: Energy balance occurs when energy intake (measured in kilocalories) equals total energy expenditure (RMR + physical activity + thermic effect of food), with gains and losses occurring when there is an imbalance. A gain of one pound occurs when approximately 3,500 calories are consumed in excess of energy needs.

obesity and cancer risk, recurrence, and mortality; (iv) interventions that promote weight loss and negative energy balance as a means of cancer control; and (v) future directions. A review of these topics is reported herein.

Energy balance

Historically, cancer has been a disease associated with cachexia (hypermetabolic state marked by anorexia and profound wasting), a problem that remains today for more advanced cancers (12). However, with more cancers diagnosed at earlier stages when cure is possible and with the discovery that more cancers are being initiated or promoted by obesity (especially against the backdrop of the obesity epidemic), it is positive—rather than negative—energy balance that seems to be the more prevalent problem.

Obesity results from chronic energy intake in excess of expenditures. Figure 1 illustrates the complex dynamic nature of energy balance in which intake (defined as absorbable energy, measured in kilocalories) is gauged against the energy demands of the body. Energy expenditure comprises 3 components: (i) resting metabolic rate (RMR), the energy required for normal body processes, which accounts for the majority of energy needs; (ii) thermic effect of food, the relatively minor amount of energy needed to digest and metabolize food; and (iii) physical activity, a moderate, but readily modifiable, constituent of energy expenditure. Theoretically, body weight shifts with every calorie of imbalance, with a total positive imbalance of 3,500 kcal promoting (or resulting in) a 1-pound increase in body weight. This simplistic model ignores differences in body composition (i.e., body stores of lean tissue, adipose tissue, stored glycogen, and body water) and the dynamic state of body composition in which increases in lean mass occur as one exercises (especially resistance training) or decreases as with sarcopenia resulting from cancer treatments, such as chemotherapy (13). This is important because lean body mass determines RMR. This relationship is worth noting because it is unknown whether obesity per se drives cancer progression, or whether components of energy balance (i.e., too much energy consumed or too little energy expended) have a greater impact, and which factors hold promise for cancer control.

Potential mechanisms by which positive energy balance contributes to cancer progression

All of the putative mechanisms whereby obesity drives the progression of cancer are not yet known; however the process is acknowledged as complex. Earlier work focused on associations between obesity and higher levels of free circulating sex hormones (e.g., estradiol) and their impact on hormonally linked cancers (14–17), such as cancer of the breast. Now a multitude of other mechanisms are being elucidated. Preclinical data indicate that energy balance may affect genomic instability, dysregulated growth signaling and cellular energetics, inhibition of apoptosis and immune surveillance, and angiogenesis (18). Moreover, myriad factors interact in an intricate signaling network to accelerate neoplasia. Data now exist for several factors including energy-driven signaling via insulin, insulin-like growth factor-1 (IGF-1; cross-talk with EGF), phosphatidylinositol 3-kinase, and AMP-activated protein kinase, and many other entities. Components of insulin resistance syndrome have been well studied in both breast (19–23) and colorectal cancer (24–31). For example, in nondiabetic breast cancer patients, higher levels of fasting insulin have been associated with a 2- to 3-fold increased risk of mortality (19–23, 32). Overexpression of insulin receptors, notably the fetal insulin receptor (IRα) on breast cancer cells, provides a biologic basis for this effect, as expression of total insulin receptor or phosphorylated IGF-1 receptor/insulin receptor are associated with poorer breast cancer outcomes (33). Parallel findings are reported for colorectal cancer and suggest that physical activity, adiposity, and diet influence insulin and IGF levels, which subsequently stimulate growth and inhibit apoptosis of micrometastases—a presumed cause of recurrence (34).

Moreover, adipose tissue, once thought to be inert, is now recognized as metabolically active and a source of inflammatory modulators. The adipokine, leptin, enhances the production of inflammatory factors, such as interleukin-6 (IL6), IL1β, and TNFα that lead to the activation of NFkB and downstream effects that signal through the mTOR to initiate transcription. This cascade also seems influenced by sex hormones (estradiol and testosterone) and growth factors, notably VEGF. In contrast, increased adiposity is associated with lower levels of adiponectin, an adipokine that induces apoptosis. Evidence for these mechanisms has been noted specifically in breast and colorectal cancer (35, 36). More detail on the mechanisms by which obesity drives cancer progression,

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as well as considerations and potential models to best study the relationship between energy balance and cancer are covered in another report emanating from this IOM Workshop.

Association between energy balance (body weight, energy restriction, and increased physical activity) and cancer recurrence and survival

Preclinical studies. Given the difficulty in accurately assessing energy intake and energy expenditure in humans, fewer studies have addressed the individual components of energy balance in relation to cancer progression. However, there is substantive research in animal models. The first reported study of energy restriction was conducted in rodents by Moreschi in 1909 (37). In a transplanted tumor model, energy restriction was found to significantly reduce tumor growth as compared with an *ad libitum* control. Over the past century, similar experiments in a variety of animal models and using chemically induced carcinogenesis, as well as transplanted tumors and/or cells, have produced profoundly consistent results: energy restriction inhibits neoplastic progression (38, 39). However, body weight is lower in the energy-restricted animals, and it is not possible to disentangle whether it is energy restriction or reduced adiposity that decreases tumor burden. Nor is it clear whether less extreme energy restriction or that which is instituted in obese animals after the onset of cancer would have similar effects–both of which have greater clinical relevance.

Animal studies of physical activity are more uncommon and have yielded inconsistent findings, with most studies addressing carcinogenesis rather than cancer progression. In the few studies of transplanted tumors or cell lines, 2 (in breast and pancreatic cancer) showed inhibition of tumor growth with increased physical activity (40, 41), one (in breast cancer) showed no difference (42), and one (in colon cancer) reported harm (43). Control of energy intake (40, 41) versus *ad libitum* feeding (42, 43) may have contributed to discrepant findings. Although not in a cancer model, Padovani and colleagues (44) attempted to disentangle energy balance factors by directly comparing the effects of energy restriction to increased energy expenditure on gene expression. Their 6-week study in C57B/6 mice showed that mammary gland gene expression profiles of mice assigned to increased physical activity versus controls varied with regard to 45 genes; in contrast, the mice assigned to energy restriction varied by 425 genes, with an overlap seen in only 3 genes. Thus, at least in animal models, the biologic pathways affected by energy restriction appear quite different than those associated with energy expenditure, and the net effect of energy balance and obesity are likely to even further complicate these associations.

Observational studies. Direct measures of body composition, such as dual energy X-ray absorptiometry and computed tomography (CT) are costly and cumbersome; thus most human studies of obesity and prognosis have used weight or BMI with an assumption that excess adipose tissue comprises much of the added mass. Waist circumference (a measure of central adiposity) also is frequently assessed to improve precision of the classification of obesity but also to be able to evaluate whether the location of excess adiposity differently influences outcomes. In the growing body of survivorship research, data suggest that increasing BMI portends less favorable outcomes, not only with respect to cancer-specific recurrence and survival (stated above) but also for comorbidity (e.g., diabetes, cardiovascular disease (CVD), and poorer post-surgical wound healing and infection) and overall survival (45, 46). As with all cancer-related research, controlling for cancer stage, grade, and treatment are of paramount importance; however, as weight loss can be a symptom of recurrent cancer, it is also important to distinguish whether changes in weight are volitional versus involuntary. A review of evidence from observational studies in breast, prostate, and colorectal cancer follows.

In a recent meta-analysis of more than 40 studies of women diagnosed with breast cancer, Protani and colleagues (7) reported a modest, but statistically significant and clinically relevant increase in all-cause and breast cancer–specific mortality in obese versus nonobese women [HR, 1.33; 95% confidence interval (CI), (1.21–1.47) and 1.33 (1.19–1.50), respectively], regardless of whether obesity was characterized by BMI or waist:hip ratio, whether the study was observational or a trial of therapy, whether patients were premenopausal, postmenopausal or both, and whether the study was published before 1995 or after (when anthracycline/taxane-based adjuvant therapies were more commonly used). Moreover, emerging evidence suggests the adverse effects of obesity on breast cancer outcomes persist long term (6, 35). Obesity has been consistently associated with prostate cancer mortality in cohort studies of men without the disease at baseline (47–49). Recent studies suggest that obesity around the time of diagnosis and afterwards, as well as weight gain are associated with poorer outcomes among men diagnosed with the disease (5); these findings are independent of the higher incidence of advanced stage and high Gleason sum disease seen in obese compared with nonobese men. For colorectal cancer, data have only recently emerged and suggest mixed results. Most studies of adiposity and outcomes in nonmetastatic colorectal cancer show poorer outcomes solely in extremely obese patients, that is, BMI $\geq$ 35 kg/m^2 (8, 50–55). In a cohort of approximately 4,000 stage II–III colon cancer patients participating in 4 NCI-sponsored adjuvant therapy trials, BMI $\geq$ 35 kg/m^2 was associated with a 38% increased risk of recurrence and a 36% increased risk of disease-specific mortality (53). Two studies have assessed change in weight postdiagnosis or postdiagnosis BMI on cancer recurrence and survival and neither found an association (51, 56), with the more recent study by Campbell and colleagues suggesting that obesity prediagnosis is most important.

To date, no observational studies assessed energy intake using validated methods, though several have evaluated associations between dietary factors and cancer

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outcomes, especially in breast (57, 58), colon (59), and prostate cancers (60–62). However, few consistent relationships have emerged for intakes of specific micro- or macronutrients, or dietary patterns.

Several reports suggest that physical activity after cancer diagnosis is associated with better cancer-specific and overall survival in individuals diagnosed with early-stage breast, prostate, and colorectal cancers (63–67). Seven prospective cohort studies, including almost 20,000 individuals in aggregate, examined the relationship between physical activity after breast cancer diagnosis and recurrence- and disease-specific mortality (63, 68–73). Six of the 7 studies suggest that women who participate in modest levels of physical activity postdiagnosis have significantly better outcomes as compared with sedentary women. For example, women who engage in >9 MET-h/wk of physical activity (equivalent to walking at an average pace for 3 h/wk) had a 50% lower risk of breast cancer death, and all-cause mortality, than women who were inactive (engaging in <1 hour of moderate-intensity activity/wk; ref. 63). Similar findings have been reported in colorectal cancer survivors, in whom participation in ≥18 MET-h/wk of postdiagnosis physical activity was associated with a 50% lower risk of cancer recurrence and/or mortality (64, 65, 74). For prostate cancer, a 46% reduction in overall mortality was observed among prostate cancer survivors who walked for ≥90 min/wk, and reductions of 61% and 49% were seen respectively in prostate-specific and all-cause mortality in men who engaged in ≥3 h/wk of vigorous activity (66). Despite this observational evidence, the impact of increasing physical activity after cancer diagnosis upon prognosis has yet to be tested in randomized trials. However, small interventional studies in breast cancer survivors have shown that physical activity leads to improvements in serum insulin and other biomarkers linked to breast cancer risk and prognosis (75, 76). Further research is needed to understand the impact of physical activity on cancer outcomes, especially as observational studies are unable to discern cause and effect, and exercise clusters with many other health behaviors, including healthier diets and treatment adherence (77). The Colon Health and Life-Long Exercise Change (CHALLENGE) trial is one such trial and will be described in a subsequent section.

In summary, obesity, excessive energy intake, and physical inactivity may be important modifiable risk factors for poor cancer outcomes. However, a few critical limitations of the extant research should be acknowledged. Notably, few studies have complete data on specific cancer treatment regimens. With early studies showing that obese breast cancer patients receive less adequate doses of chemotherapeutic agents, treatment stands as an important confounder or effect modifier (78). Although new guidelines have led to improved dosing among obese patients, the uptake of these recommendations is inconsistent, especially across community-based practices. Practice patterns also are influenced by the presence of comorbidities, which are highly prevalent among cancer patients as cancer is a disease of aging. An example that well illustrates this complex situation is provided by diabetes mellitus, an obesity-related comorbid disease that reportedly occurs in 5% to 17% of individuals with breast, colon, or prostate cancer (79). Here, the risk of death may be 2- to 3-fold higher compared with mortality in cancer patients without co-occurring diseases (79), with previous studies purporting that this may be attributed either to less aggressive cancer treatment among diabetics (80) or to less aggressive glucose control among those diagnosed with cancer (81). Moreover, few studies have controlled for medication use, despite emerging evidence that some agents, for example, metformin or insulin, may have direct effects on cancer outcomes (82). Thus, much more research is needed to resolve the many knowledge gaps that remain at the interface of energy balance and cancer (Table 1). Consideration of several methodologic and inferential issues is key in moving the science forward most expeditiously (Table 2).

Weight loss, diet, and physical activity interventions

Lessons learned from weight loss interventions in the general population. During the past 40 years, the prevalence of obesity among U.S. adults has more than doubled—from 15% to 35% (9, 83). The increased risk of chronic disease morbidity and mortality resulting from obesity has prompted efforts to develop effective weight loss interventions for the general population. The lessons learned from these interventions provide a backdrop for their translation to cancer survivors. Interventions that have been broadly tested in the general population include lifestyle modification, pharmacotherapy, and bariatric surgery.

A comprehensive program of lifestyle modification, which includes diet, exercise, and behavior therapy, is the most broadly recommended approach for weight loss (84). The goal of this approach is a reduction in body weight of at least 7% to 10%, which has been shown to improve several obesity-related conditions, such as diabetes mellitus and risk of CVD (84). The U.S. Preventive Services Task Force recommends that clinicians screen all adults for obesity and offer intensive (at least monthly) counseling and behavioral interventions to promote sustained weight loss (85, 86). Numerous randomized controlled trials have concluded that achieving an energy deficit of 500 to 1,000 kcal/d (sufficient to induce a 1–2 pound/wk loss) is a central component of any weight loss regimen, and that varying the macronutrient content is not as important as overall energy intake (87–89); though for cancer survivors, eating a diet that is nutritionally sound and which meets cancer prevention guidelines is advised (3, 90). Long-term patient–provider contact and high levels of physical activity (200–300 min/wk of brisk walking) are necessary to maintain lost weight (89, 91, 92). The Diabetes Prevention Program (DPP; ref. 93) and the Look AHEAD study (94, 95) are 2 of the largest lifestyle modification weight loss trials. The DPP randomized 3,234 obese adults with impaired glucose tolerance to

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usual care, metformin, or a lifestyle intervention. Lifestyle intervention participants were instructed to (i) reduce their energy intake by 500 to 1,000 kcal/d (by decreasing portion sizes, fat, and sugar), (ii) increase fruit and vegetable intake, and (iii) exercise for >150 min/wk (96). They kept records of their weight, food intake, and physical activity, which they reviewed regularly with dietitians. The study showed that a mean loss of 7% of initial weight reduced the risk of developing type 2 diabetes by 58% compared with placebo and by 31% compared with metformin (over an average follow-up of 2.8 years). The Look AHEAD study is now testing whether a 7% or greater weight loss in overweight/obese adults with type 2 diabetes will reduce cardiovascular morbidity and mortality over a 13.5-year follow-up (94, 95). In the first year, lifestyle participants lost 8.6% of their initial weight and achieved substantial improvements in fitness and CVD risk factors, compared with usual care. Four-year weight losses were 4.7% and 1.1%, in intervention and control groups, respectively (97). Further follow-up is needed to determine whether improvements in CVD risk factors in the lifestyle group translate into reduced morbidity and mortality.

Pharmacotherapy is an option for individuals with a BMI > 30 kg/m^2 (or >27 kg/m^2 with comorbid conditions; ref. 84). At present, orlistat is the only weight loss medication approved for long-term use (98). It produces losses that are 3 kg greater than placebo (99, 100). The largest weight losses are obtained when pharmacotherapy is combined with lifestyle modification (101, 102).

For those severely obese, bariatric surgery (including vertical-banded gastroplasty, gastric bypass, and laparoscopic adjustable gastric banding) offers the most assured approach to weight loss as assessed by both short- and long-term outcomes (101, 103, 104). Weight loss at 1 to 2 years may be as high as 32% of initial weight. At 10 years, weight loss averages 14% to 26%, depending on type of surgery (101). Enthusiasm for this success is tempered, in part, by limits to the proportion of the population for whom surgery is recommended, that is, 5.1% of the U.S. population with a BMI > 40 kg/m^2 (84, 105), as well as attendant risks, for example, mortality rates of 0.1% to 0.3% and complication rates of 4% to 9% (106, 107). Of particular interest in the context of this review, a diagnosis of cancer within the past 5 years has generally been a contraindication to bariatric surgery. Longitudinal data in obese populations, however, shows that weight loss accomplished by surgery reduces cancer incidence and mortality compared with people who have not undergone bariatric surgery. Most of these studies reported risk estimates for cancer incidence rather than cancer mortality. The numbers of women enrolled in these studies of bariatric surgery are much larger than the numbers of men, which may be one reason that statistically significant associations with cancer incidence and mortality have been observed predominantly for women (108). The one study that reported HRs for the effect of bariatric surgery on cancer mortality observed a 50% reduction in cancer mortality for women (103). All of these studies have been based on obese patients, very few of whom had any prior history of cancer, and none were undergoing active treatment for cancer. Whether the effects of bariatric surgery on cancer mortality are due entirely to a reduction in cancer incidence or whether it confers additional survival benefit postdiagnosis are yet to be determined (101, 109). This raises the intriguing concept that weight loss may be beneficial in contributing to short- and long-term survival in cancer patients.

Issues and challenges for interventions that target cancer survivors.

The promotion of weight loss and lifestyle change in cancer survivorship can present several challenges unique to this growing population. Side effects and posttreatment symptomatology are common and can interfere with patients' abilities to engage in a weight loss intervention and their consequent success. For example, weight loss may have to be postponed until primary treatment is complete to assure adequate immune function; moreover, risks for infection in gym-based programs must be considered (110). Another consideration is chemotherapy-induced sarcopenia that can be exacerbated by rapid weight loss (exceeding 2 pounds/wk) via regimens that are focused solely on diet (13)–thus reinforcing the need for multicomponent interventions that incorporate exercise (especially resistance training). Fatigue and changes in appetite and taste sensation are often reported by survivors, while body image concerns may be prompted or exacerbated by the impact of treatment (111–114). However, in several cancer patient groups, studies have shown that patients who continue or engage in physical activity following diagnosis experience less fatigue (115). Furthermore, some evidence suggests that engaging in physical activity may reduce the likelihood of experiencing adverse treatment side effects and increase compliance with therapy (115). Disease, treatment, or patient characteristics may necessitate appropriate screening and adaptations of exercise involvement to assure that fractures, musculoskeletal injuries, and cardiac risk are minimized (115). In addition, some patients will experience psychologic distress (116), for example, symptoms of depression and anxiety, which can impair motivation and engagement in a lifestyle-based intervention. Importantly, individuals diagnosed and treated for cancer who succeed in losing weight may find that intentional weight loss is perceived by some individuals as indicative of disease recurrence or progression and a cause for concern. Although weight management and lifestyle change are recommended in overweight and obese survivors, the impact of weight loss on disease outcomes has not been shown. However, given the documentation of the common occurrence of obesity-related comorbid disease among many cancer survivors and the increased risk of death in these patients, it is hypothesized that weight loss in overweight and obese survivors would be beneficial.

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Table 1. Summary of the evidence and evidence gaps about research on energy balance and cancer recurrence and survival

Evidence	Evidence gaps
Energy balance and cancer risk	
➢ Consensus for direct associations between obesity and the incidence of the following cancers: endometrial, colorectal, renal, esophageal, pancreatic, and postmenopausal breast. ➢ Accumulating evidence for direct associations between obesity and the incidence of cancers of the ovary, gallbladder, thyroid, liver, and aggressive forms of prostate cancer, as well as non-Hodgkin lymphoma. ➢ Weight loss during adulthood is associated with a reduced incidence of postmenopausal breast cancer. ➢ Weight gain during adulthood (adult onset obesity) is associated with an increased incidence of postmenopausal breast cancer and colon cancer. ➢ Obesity is a risk factor for cancer-related mortality from the following cancers: breast, colon, and rectum, cervix, esophagus, gallbladder, kidney, liver, multiple myeloma, non-Hodgkin lymphoma, ovary, pancreas, prostate, stomach, and uterus.	➢ What is the impact of obesity on the incidence of other cancers or cancer subtypes (inclusive of childhood cancers)? ➢ What are the effects of a lifetime of obesity on cancer risk and outcomes?
Energy balance and cancer recurrence and promotion	
➢ Obesity at diagnosis is a poor prognostic factor for cancers of the breast, colon, and prostate.	➢ What is the effect of obesity at the time of diagnosis on subsequent prognosis for cancers other than breast, colon, and prostate? ➢ Are there differential effects of obesity on overall and disease-specific survival by gender, race, ethnicity, comorbidity status (and associated treatment), or various genotypes? ➢ What are the comparative contributions of increased adiposity, energy intake, or decreased physical activity on cancer recurrence and disease-specific mortality? ➢ How do obesity-driven events such as stimulated growth factors, cytokines, adipokines, and hormones interact with obesity-related clinicopathologic factors, such as later stage at diagnosis, reduced treatment efficacy, or contribution of comorbid factors (e.g., diabetes) to affect disease-specific and overall outcomes? ➢ What is the impact of weight change during various stages of neoplasia, for example, preneoplastic lesions, early-stage nonaggressive cancers, later stage aggressive cancers, during active treatment, during the course of disease-free survivorship, and after recurrence or living with active progressive disease? ➢ How does physical activity during active treatment affect various treatment modalities, including dosing, (dis) continuation of therapy, and efficacy? What is the effect on tumor biology, including angiogenesis and the tumor microenvironment?
Mechanisms of energy balance and cancer promotion	
➢ Several mechanisms have been identified whereby energy balance may affect cancer promotion, including those associated with inflammation, sex steroids, growth factors, and energy-related signaling.	➢ What are the dominant mechanisms and cross-talk between pathways whereby energy balance affects neoplastic progression, and do they vary according to cancer type and stage?

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Table 1. Summary of the evidence and evidence gaps about research on energy balance and cancer recurrence and survival (Cont'd)

Evidence	Evidence gaps
➢ Obesity-associated metabolic syndrome is associated with some forms of cancer, for example, breast cancer and may support the use of energy-related mimetics, such as metformin, as adjunctive treatment.	➢ Are there additional, yet not well described, effects on molecular pathways, for example, related to DNA repair and the tumor microenvironment? ➢ Are there discrepancies in cancer–related pathways between animals and humans? ➢ What are the most appropriate preclinical models to study energy balance and cancer? What are the most appropriate biomarkers to assess within and across models? ➢ Do agents that target energy-specific pathways, such as metformin, effectively hinder cancer progression?
Energy intake and physical activity and their comparative effects on cancer	
➢ Varying levels of evidence exist about the role of energy balance (and each of its separate components) on cancer incidence and outcomes. - Energy restriction (20%–25% of *ad libitum* intake) reduces the risk of cancer and cancer progression in animal models. - Exercise interventions in animal models have produced mixed results with regard to cancer development and progression. - Human observational data suggest that increased physical activity is associated with lower risk of breast and colorectal cancer, and reduced risk of progression of these cancers.	➢ Does energy restriction inhibit cancer progression in humans? What level of restriction is necessary and is negative energy balance best accomplished via intermittent fasting or continual energy restriction? ➢ Do physical activity interventions, either in animal models or in humans, inhibit tumor burden or cancer progression?
Weight loss interventions and their applications among cancer survivors	
➢ Much is known about weight loss in healthy populations. - Losses of 5%–10% improve risk factors (e.g., glucose control, serum lipids, and blood pressure) that are important for other chronic diseases (e.g., diabetes and CVD). - A 3-pronged approach of energy restriction, increased physical activity, and behavior modification is recommended, and evidence also supports the use of pharmacologic agents in select populations. - A growing body of evidence supports bariatric surgery to promote long-term weight control in select populations. - Diet composition does not seem to mediate weight loss success. - Greater weight loss is seen with preportioned, structured meals, and meal replacements. - Greater adherence is observed with more-intensive vs. less-intensive interventions. - A combination of aerobic and strength training physical activity seems most beneficial in improving body composition.	➢ What is the effect of weight loss and long-term weight control on cancer outcomes? What are potential moderators (e.g., treatments, other medications)? ➢ Are pharmacologic agents commonly used to control diabetes (energy restriction mimetics) helpful in controlling cancer, and what is their comparative effect when tested against energy restriction and/or increased physical activity? ➢ What are the most effective interventions for achieving and maintaining weight loss among cancer survivors and are there differential effects on cancer outcomes that are dependent on the mode of instilling negative energy balance? ➢ What duration, dose, and frequency of exercise, as well as mode constitute the optimal exercise regimen for creating long-term weight control among cancer survivors? ➢ Are there potential adverse effects of intervening in cancer survivors? For example, are there survivors who should not do vigorous exercise or lose weight? ➢ Are there dose responses for weight loss and physical activity? Are there thresholds beyond which the amount or rate of weight loss is not deemed safe for cancer survivors? ➢ Are there independent effects of diet composition on cancer-related outcomes?

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Table 1. Summary of the evidence and evidence gaps about research on energy balance and cancer recurrence and survival (Cont'd)

Evidence	Evidence gaps
➢ From the weight loss interventions that have been conducted among cancer survivors, many of the same elements (i.e., energy restriction, aerobic and strength training exercise, and behavior modification with cognitive restructuring) seem important, as is grounding in behavioral theory (e.g., social cognitive theory, theory of planned behavior), which endorse tenets such as social support, incremental goal setting with reinforcement, and help with overcoming barriers. ➢ Many cancer patients gain weight after diagnosis and experience adverse changes in body composition [i.e., loss of lean body mass (muscle and bone) and gain of adipose tissue]. Weight gain is associated with chemotherapy, increased BMI at diagnosis, and younger age, and is partially explained by decreased physical activity during treatment.	➢ Are there other causes of treatment-related weight gain among cancer patients, for example, changes in methylation in promoters of energy-related genes? Which chemotherapeutic agents are associated with the greatest gains in weight and/or adiposity? ➢ What are the effects of weight gain on the tumor microenvironment? ➢ What interventions are best able to ameliorate treatment-related weight gain? ➢ What are the most cost-effective strategies to promote weight control in cancer survivors? ➢ Many questions remain with regard to the dissemination of weight loss interventions: - Which cancer survivors should receive them? - Who will deliver them? - Who will pay for them?

Prior energy balance interventions in cancer survivors

Accrual, retention, adherence, and scope of research. To date, most diet and physical activity interventions have been conducted in well-educated, non-Hispanic white, breast cancer survivors. Survivor accrual into energy balance interventions requires considerable time and effort, and achieving high retention and adherence is challenging, underscoring the importance of detailed reporting of characteristics of respondents versus nonrespondents, completers versus drop-outs, and participants with high versus low adherence (117). The ability of intervention trials to successfully recruit and retain a representative sample of cancer survivors, with minimal attrition and high adherence rates, is essential for the eventual translation and dissemination of effective interventions more broadly, including underrepresented subgroups, such as lower socioeconomic status, rural, and racial–ethnic minority survivors.

Physical activity interventions in cancer survivors

Few physical activity trials have focused on survival because of the extended duration of study and sample sizes required, or on weight loss, presumably because of the modest effects of physical activity alone on weight loss in other populations (118). However, physical activity trials have shown improvements in many health outcomes in cancer survivors, including health-related fitness (119), fatigue (120), depression (121), and quality of life (122). Moreover, there is emerging evidence that stronger effects accrue for physical activity interventions that are supervised (121, 122), facility based (121), at least of moderate intensity (120, 122), $\geq$30 min/session (121), and delivered after completion of primary curative treatment (119).

On the basis of the strong observational data on the benefits of physical activity after a colorectal cancer diagnosis, a multinational trial in Canada and Australia, the CHALLENGE trial, was developed. The goal of the trial is to determine the effects of a 3-year structured and supervised physical activity intervention on disease outcomes in 962 high-risk stage II–III colon cancer survivors who have completed adjuvant chemotherapy within the previous 2 to 6 months (123). The primary endpoint is disease-free survival and secondary endpoints include patient-reported outcomes, health-related fitness, biologic correlative markers, and an economic analysis. The trial is currently open to accrual and incorporates intervention approaches shown effective. Like most other trials of physical activity, CHALLENGE is not aimed at weight loss, but body weight status will be monitored and explored in relation to disease outcomes.

Diet and weight loss interventions in cancer survivors

The Women's Intervention Nutrition Study (WINS; ref. 124) and the Women's Healthy Eating and Lifestyle (WHEL; ref. 125) trials, conducted among early-stage breast cancer survivors, tested the effects of dietary interventions on cancer recurrence and survival, although neither was directly aimed at energy restriction. The WINS intervention (n = 2,437, enrolled within one year of diagnosis), promoted a low-fat diet to only 15% of energy intake through individualized dietary counseling provided by registered dietitians (124). Self-reported fat intake approximated 20% of energy intake in the intervention group versus 29% of intake in the control group at 12 months. At 5 years, women assigned to the low-fat intervention lost an average of 6 pounds (~4% of initial

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Table 2. Design and interpretation concerns for studies examining energy balance and cancer recurrence and survival

- Determination of the optimal cancer outcome to evaluate, for example, recurrence, progression to metastases, or cancer death. The decision rests on the following factors:
  - An ability to capture biology and the greatest clinical impact
  - The type of treatment and management a patient receives, which is partly dependent on the pathologic characteristics of the tumor at diagnosis
  - The time required to observe outcomes
- Inclusion of a comparison group to account for social interaction/placebo effects, which may be particularly important for trials targeting patient-reported outcomes.
- Control for confounding by pathologic characteristics (e.g., cancer stage, and grade); if obesity is associated with worse pathologic characteristics of the cancer, and these characteristics are strong prognostic factors, then adjustment is essential to determine whether obesity independently influences outcome.
- Control for confounding or effect modification for factors that may co-occur with obesity, for example, physical activity, energy intake, diabetes and other comorbid conditions, and smoking
- Knowledge that treatment and management of cancer might affect the interpretation of the results if:
  - The presentation or selection of treatment options varies by weight status
  - The treatment success varies by weight status, for example, whether the chance of positive surgical margins and thus recurrence varies by weight status
  - Potential for reverse causation as some treatments, for example, hormonal therapy, can lead to an increase in body fat accumulation, especially centrally, and metabolic perturbations
- Recognition that the effects of energy balance on cancer may differ depending on:
  - Cancer type and stage
  - Treatment
  - Race/ethnicity of the host
  - Body fat distribution
  - Other cofactors (e.g., smoking, comorbidity, medications)
  - Awareness that findings of studies conducted in non-Hispanic white survivors of nonmetastatic breast, prostate, or colorectal cancers (i.e., most studies conducted to date) may not generalize to survivors of other race/ethnicity, cancer type, or advanced cancer.
- Awareness that the effects of adiposity on cancer may differ depending on:
  - Body fat distribution and extent of body fatness
  - Volitional vs. nonvolitional weight loss
  - Rapid vs. slower weight change
  - Intermittent vs. continual exposure
- Realization that the effects of negative energy balance on cancer may differ depending on:
  - Diet composition
  - Type of physical activity
  - The magnitude of energy deficit
- Awareness that the measurement of diet and physical activity is difficult, and discrepancies in methods pose a challenge for pooling of data or carrying out meta-analyses.
- Consideration of the relationships between obesity, comorbidity, and treatment (which may or may not be independent) in the analysis and interpretation of results.
- Consideration within the study design and analysis to reduce and account for potential measurement error (e.g., energy intake, physical activity, and obesity).
- Lack of control for all components of energy balance (i.e., both energy intake and physical activity, as well as BMI).
- Lack of characterization of the study population about accrual (enrollees vs. larger pool of cancer survivors) and attrition (completers vs. dropouts).
- Adherence and long-term change in behavior.
- Adequate power to detect significant associations.

weight) compared with controls. There were significantly lower rates of recurrence observed in the intervention arm overall (HR, 0.76; 95% CI, 0.60–0.98) and particularly among women with estrogen receptor–negative disease (HR, 0.58; 95% CI, 0.37–0.91). In contrast, the WHEL intervention ($n = 3,088$, enrolled up to 4 years postdiagnosis), used telephone-based dietary counseling to promote a daily intake of 5 vegetable servings plus 16 ounces

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of vegetable juice or equivalent, 3 fruit servings, 30 g fiber, and 15% to 20% energy from fat (125). Participants randomized to the dietary intervention significantly increased intake of fruit and vegetables and decreased intake of fat, with no differences observed in weight change between arms. After a median follow-up of 7.3 years and 518 relapse events, there were no between-arm differences in recurrence (16.7% vs. 16.9%) or survival (10.1% vs. 10.3%). Whereas the high fruit and vegetable intake of WHEL participants at baseline may have undermined the ability of the trial to detect between-arm differences, the differential in weight change observed between the 2 trials also may have contributed to the discrepant findings.

Similar to WINS, other dietary interventions resulted in modest (2% to 3% of initial body weight) yet significant weight loss as a consequence of lower fat, high fruit and vegetable diets, for example, the FRESH START trial conducted in 543 newly diagnosed breast and prostate cancer survivors (126). In addition, weight gain prevention interventions have also been evaluated during adjuvant chemotherapy for breast cancer, when weight gain is common (127–129). However to date, only 6 diet or diet and exercise intervention trials have pursued weight loss as a specific aim (130–135).

Earlier studies relied on individual dietary counseling to deliver guidance on energy restriction (130), whereas more recently group-based support has been used to bolster individualized approaches (131) or used on its own. For example, in a year-long study of 48 obese stage I–II breast cancer patients, Djuric and colleagues found weight losses of <1% of initial weight in controls, 8.4% of initial weight with individualized counseling, and 9.8% of initial weight when individualized counseling was paired with Weight Watchers group sessions. Two other group-based interventions in breast cancer survivors, that is, the Healthy Weight Management (HWM) Study ($n = 85$; ref. 132) and the Survivors Health And Physical Exercise (SHAPE) trial ($n = 258$; ref. 135) tested the impact of a cognitive behavioral weight loss program plus telephone counseling against a wait-list control. Both interventions resulted in significant improvements in physical activity and weight loss, with the HWM producing an 8% loss in initial weight at 12 months, and SHAPE invoking a 4.5% loss of initial body weight at 18 months. The weight loss and increased physical activity were also associated with favorable changes in self-esteem, depression, and serum concentrations of sex hormone–binding globulin, estradiol, bioavailable estradiol, insulin, leptin, and total and low density lipoprotein cholesterol. Although far less intensive and the only trial to date to promote weight loss in a broad population of survivors, the Reach-out to Enhance Wellness in Older Survivors (RENEW) trial tested a mailed print and telephone counseling intervention in 641 elderly (age 65+), overweight, or obese, long-term (5+ years postdiagnosis) survivors of breast, prostate, and colorectal cancer (133). Aims of this trial were to reduce the trajectory of functional decline and incur a slow rate of weight loss (<1 pound/wk) via a portion-controlled, low-energy density diet (i.e., increased fruit and vegetables, low saturated fat), and increased physical activity. At 12 months, the intervention group as compared with a wait-list control, significantly reduced the rate of functional decline and improved physical activity, dietary behaviors, and overall quality of life. The intervention group also had an average weight loss of 3% of initial weight, which was sustained over a 2-year period. Factors that likely contributed to the intervention's success were its strong reliance on behavioral theory and intervention contact over an extended period (136).

Elements of each of these trials, as well as DPP and Look Ahead are incorporated into 2 current trials. The Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) trial is a multisite trial designed to promote and sustain a 7% weight loss over a 2-year period in 800 overweight or obese stage Ic-III breast cancer survivors. The study is strategically designed as a vanguard component of a fully powered trial of at least 2,500 women with breast cancer recurrence endpoints. The group delivered intervention addresses breast cancer–specific issues and promotes an energy-restricted diet, plus increased physical activity, behavioral strategies, cognitive restructuring, skills to facilitate and maintain good choices, social support, self-nurturing, and body image and self-acceptance. In the Lifestyle Intervention Study Adjuvant (LISA), a 2-year, telephone-based intervention involving 19 contacts, data showed a significant weight loss in the intervention ($n = 165$) versus control ($n = 158$) arms, with the following differences noted over time: –4.7 versus –0.2 kg at 6 months; –5.5 versus –0.7 kg at 12 months; and –3.8 versus –0.3 kg at 18 months (134). A full scale adjuvant trial in the North American Breast Cancer Intergroup has been proposed.

In summary, results from diet and weight loss studies conducted to date show that cancer survivors are motivated and able to make dietary and lifestyle modifications. Individualized counseling (in person or by telephone), group sessions, and tailored mailed materials that are backed by behavioral theory have all proven effective.

Are weight loss and physical activity prescriptions controversial for cancer survivors? Until recently, most clinicians focused only on the risk for cancer recurrence and seldom counseled their patients about other chronic or comorbid conditions. As most individuals who are diagnosed with cancer are above age 60 and come to the diagnosis with comorbid conditions or acquire them as they age (137), counseling these individuals to achieve and maintain a normal weight and remain physically active as they age makes good sense clinically. Cancer and its treatment are associated with an increased risk for comorbid conditions (79, 138), and many survivors successfully treated for their cancer will succumb to heart disease, diabetes, and stroke. Interventions that can help them maintain health and well-being may also improve overall functioning, mood, and help maintain independence with aging.

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Table 3. Recommendations for advancing the field of energy balance and cancer recurrence and survival

Administrative

- Expand grant review panel capacity to reflect scientific expertise to adequately review current research issues in cancer survivors, including biologic and behavioral dynamics, such as the impact of energy balance.
- Strengthen resources to share innovative measures and methodologies to foster cutting-edge science.
- Network with public and private organizations to create innovative and relevant research opportunities; strengthen translational research to bridge scientific discovery to improvements in public health.
- Establish a better understanding of cost-effectiveness of approaches. Increase research on economic questions as they relate to obesity and cancer.
- Promote transdisciplinary training opportunities for new investigators and provide funding mechanisms that spur translational science among the entire research community.

Observational studies and intervention trials:

- Identify/develop and evaluate newer technologies and tools to deliver interventions (e.g., smart phones, tablets) and to more accurately measure diet (dietary recalls, ASA24, ecological momentary assessment (EMA) technology and physical activity (accelerometry, ACT24, EMA technology).
- Collect additional data pertinent to the evaluation of energy balance and cancer outcomes:
  - Weight (adiposity) status
  - Biologic samples (tumor and normal tissue, blood, urine, buccal cells, and others)
  - Comorbid conditions
  - Complete cancer treatment data
  - Complete data on medication-use (including over-the-counter)
- Determine whether there are differences in the association of obesity/weight gain with cancer outcomes in cancer patients by timing relative to cancer diagnosis and treatment (prediagnosis, at diagnosis/treatment, in the months and years following diagnosis/treatment, or over the life course).
- Explore the potential to pool data from existing cohorts of cancer patients to facilitate the examination of whether the effects of obesity and physical activity vary by specific subgroups of patients or tumor subtypes.
- Expand translational research with an emphasis on cancer survivors.
- Promote a transdisciplinary research focus that engages expertise from basic laboratory, clinical, environmental, public health, and community expertise.
- Integrate individual and social–environmental approaches to explain and modify energy balance–related health behaviors and cancer survivorship.
- Expand policy-specific research as it addresses obesity and energy balance behavior, and the larger systems (environment) that influence behavior change.
- Promote dissemination and implementation research to help strengthen the capacity of programs and policies to have maximum reach and impact.

Pharmacologic trials:

- Capture BMI (as well as other measures of adiposity and components of energy balance, for example, dietary intake and physical activity) within pharmacologic RCTs to analyze the impact of weight status, either synergistically or independently, on survival endpoints.
- Collect biologic samples (tumor and normal tissue, blood).
- Promote comprehensive common measures within datasets that can be used across agencies, researchers, and policy makers, and develop facile interfaces, whereby data can be seamlessly transferred.

Mechanistic studies:

- Identify and validate biomarkers for cancer recurrence and death.
- Determine the biologic mechanisms that regulate energy balance and inform the development of more effective lifestyle interventions that better reflect the biologic influence of human behavior.

Many patients and survivors find the experience of cancer a teachable moment–a time to start fresh and improve their overall health. Having made it through the rigors of cancer treatment, they may feel a sense of accomplishment and pride. However, working toward improving fitness and weight can be a lonely process, and encouragement from health professionals (e.g., providing guidance, specific strategies, and setting realistic goals) is important. Many patients also will be at risk for second malignancies (e.g., breast, colorectal or other hereditary cancer syndromes, shared risk factors, or as a sequelae of treatment) and may realize benefit from weight reduction, improved diet, and increased physical activity. Physical training has been shown to be effective for breast cancer patients with lymphedema (139), whereas obesity has been shown to exacerbate

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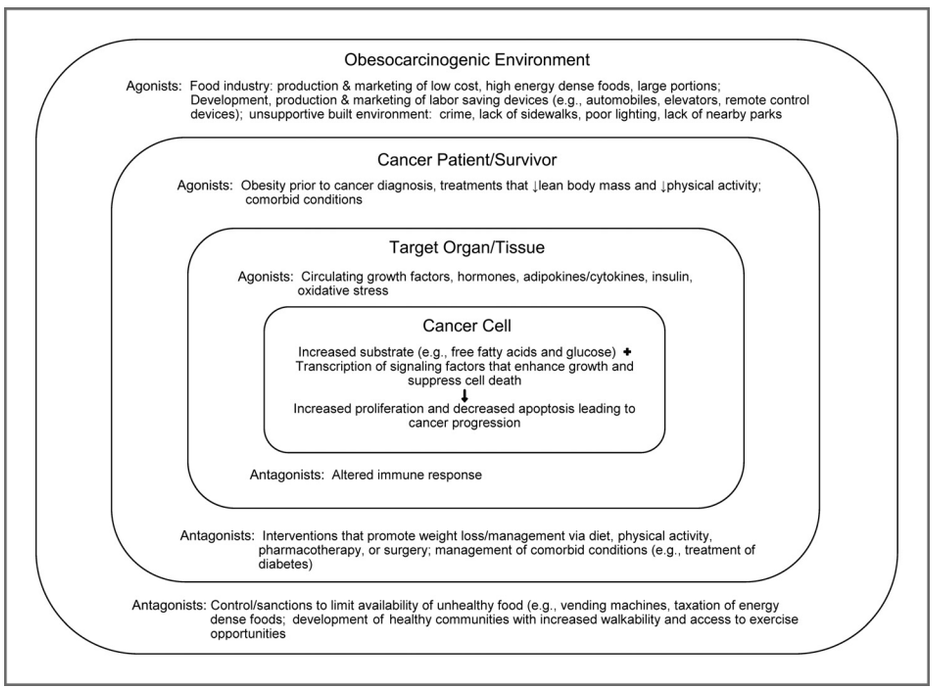

Figure 2. Cancer progression ultimately is a product of the larger environment. High-energy dense foods are foods high in energy (calories) per gram weight, for example, fried foods (high in fat), whereas fruits and vegetables are low-energy dense foods.

this condition. Thus, there may be many additional reasons for considering weight maintenance/loss programs for survivors.

Currently, we have limited evidence with regard to the cancer survival benefits related to weight loss, an improved diet, and increased physical activity; however, maintenance of a normal body weight in adulthood is not controversial as a general health recommendation and should not be ignored in this patient population. Cancer survivors may derive even more benefit, given their increased risk of comorbid conditions. As noted, in several populations of cancer survivors, several controlled trials currently are examining the benefits of weight loss and physical activity, either separately or as part of multicomponent interventions. Until these trials mature, it is reasonable to recommend prevention of weight gain in those who are not underweight, and weight loss to those who are overweight or obese, given generally accepted health benefits. At a minimum, prevention and/or management of comorbid conditions associated with obesity (e.g., diabetes, hypertension, and CVD) should be an important goal in cancer survivors.

Future directions

Despite the significant gain in knowledge with regard to energy balance and cancer recurrence and survival (Table 1), more research is needed to further elucidate this complex interface. Moving the science forward will require a multifaceted and a multi- or transdisciplinary approach. Recommendations for future research are presented in Table 3. This research will inform the development of evidence-based guidelines for clinical practice. Meanwhile, several frameworks have been proposed for the prevention and control of obesity, including health policy recommendations for changing the obesogenic environment (140, 141). As shown in Fig. 2, it is within the larger environment that cancer survivors must manage their physical activity and dietary intake, with ultimate potential effects on target tissue and cancer cells. Within each level of this socioecologic model, there are agonists and antagonists that act in opposition to either create a permissive or hostile environment for the cancer to grow, either in terms of proliferation, metastasis, or in the sheer number of recurrent cases. Thus, both researchers and society at-large need to work together to address the obesity cancer problem, discerning not only the molecular pathways by which obesity drives cancer progression but also to develop interventions acting at both individual and societal levels to control obesity in this high-risk population.

Disclosure of Potential Conflicts of Interest

T. Wadden is a recipient of commercial research grant from Nutrisystem and is also a consultant and an advisory board member of Novo Nordisk and Orexigen. E.J. Philip is a consultant and an advisory board member of Kantar Health. A. McTiernan has ownership interest (including patents) in Merck and is a consultant and an advisory board member of Metagenics.

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References

1. Hippocrates of Kos. [cited Jan 20, 2012]. Available from: http://www.platos-academy.com/archives/hippocrates.html.
2. Haslam D. Obesity: a medical history. Obes Rev 2007;8 Suppl 1:31–6.
3. World Cancer Research Fund/American Institute for Cancer Research. Second expert report, food, nutrition, and physical activity, and the prevention of cancer: A global perspective. Washington, DC; 2007.
4. International Agency for Research on Cancer. IARC Handbook of cancer prevention, Volume 6. Weight control and physical activity. Lyon, France: IARC Press; 2002.
5. Cao Y, Ma J. Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis. Cancer Prev Res 2011;4:486–501.
6. Ewertz M, Jensen MB, Gunnarsdottir KA, Hojris I, Jakobsen EH, Nielsen D, et al. Effect of obesity on prognosis after early-stage breast cancer. J Clin Oncol 2011;29:25–31.
7. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. Breast Cancer Res Treat 2010;123:627–35.
8. Sinicrope FA, Foster NR, Sargent DJ, O'Connell MJ, Rankin C. Obesity is an independent prognostic variable in colon cancer survivors. Clin Cancer Res 2010;16:1884–93.
9. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA 2012;307:491–7.
10. World Health Organization (WHO). Obesity and overweight. Fact sheet N°311. [cited Feb 2011]. Available from: http://www.who.int/mediacentre/factsheets/fs311/en/
11. Institute of Medicine. The role of obesity in cancer survival and recurrence: Workshop summary. Washington, DC: The National Academies Press; 2012.
12. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12:489–95.
13. Demark-Wahnefried W, Peterson BL, Winer EP, Marks L, Aziz N, Marcom PK, et al. Changes in weight, body composition, and factors influencing energy balance among premenopausal breast cancer patients receiving adjuvant chemotherapy. J Clin Oncol 2001;19:2381–9.
14. Brown KA, Simpson ER. Obesity and breast cancer: progress to understanding the relationship. Cancer Res 2010;70:4–7.
15. Cleary MP, Grossmann ME. Minireview: Obesity and breast cancer: the estrogen connection. Endocrinology 2009;150:2537–42.
16. McTiernan A. Obesity and cancer: the risks, science, and potential management strategies. Oncology (Williston Park) 2005;19:871–81; discussion 81–2, 85–6.
17. Pike MC, Pearce CL, Wu AH. Prevention of cancers of the breast, endometrium and ovary. Oncogene 2004;23:6379–91.
18. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74.
19. Duggan C, Irwin ML, Xiao L, Henderson KD, Smith AW, Baumgartner RN, et al. Associations of insulin resistance and adiponectin with mortality in women with breast cancer. J Clin Oncol 2011;29:32–9.
20. Emaus A, Veierod MB, Tretli S, Finstad SE, Selmer R, Furberg AS, et al. Metabolic profile, physical activity, and mortality in breast cancer patients. Breast Cancer Res Treat 2010;121:651–60.
21. Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Madarnas Y, et al. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. J Clin Oncol 2002;20:42–51.
22. Irwin ML, Duggan C, Wang CY, Smith AW, McTiernan A, Baumgartner RN, et al. Fasting C-peptide levels and death resulting from all causes and breast cancer: the health, eating, activity, and lifestyle study. J Clin Oncol 2011;29:47–53.
23. Pasanisi P, Berrino F, De Petris M, Venturelli E, Mastroianni A, Panico S. Metabolic syndrome as a prognostic factor for breast cancer recurrences. Int J Cancer 2006;119:236–8.
24. Pollak MN, Perdue JF, Margolese RG, Baer K, Richard M. Presence of somatomedin receptors on primary human breast and colon carcinomas. Cancer Lett 1987;38:223–30.
25. Guo YS, Narayan S, Yallampalli C, Singh P. Characterization of insulinlike growth factor I receptors in human colon cancer. Gastroenterology 1992;102:1101–8.
26. Koenuma M, Yamori T, Tsuruo T. Insulin and insulin-like growth factor 1 stimulate proliferation of metastatic variants of colon carcinoma 26. Jpn J Cancer Res 1989;80:51–8.
27. Bjork J, Nilsson J, Hultcrantz R, Johansson C. Growth-regulatory effects of sensory neuropeptides, epidermal growth factor, insulin, and somatostatin on the non-transformed intestinal epithelial cell line IEC-6 and the colon cancer cell line HT 29. Scand J Gastroenterol 1993;28:879–84.
28. Watkins LF, Lewis LR, Levine AE. Characterization of the synergistic effect of insulin and transferrin and the regulation of their receptors on a human colon carcinoma cell line. Int J Cancer 1990;45:372–5.
29. Giovannucci E. Insulin and colon cancer. Cancer Causes Control 1995;6:164–79.
30. Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. J Nutr 2001;131:3109S–20S.
31. Kaaks R, Lukanova A. Energy balance and cancer: the role of insulin and insulin-like growth factor-I. Proc Nutr Soc 2001;60:91–106.
32. Pritchard KI, Shepherd LE, Chapman JA, Norris BD, Cantin J, Goss PE, et al. Randomized trial of tamoxifen versus combined tamoxifen and octreotide LAR therapy in the adjuvant treatment of early-stage breast cancer in postmenopausal women: NCIC CTG MA.14. J Clin Oncol 2011;29:3869–76.
33. Law JH, Habibi G, Hu K, Masoudi H, Wang MY, Stratford AL, et al. Phosphorylated insulin-like growth factor-i/insulin receptor is present in all breast cancer subtypes and is related to poor survival. Cancer Res 2008;68:10238–46.
34. Wolpin BM, Meyerhardt JA, Chan AT, Ng K, Chan JA, Wu K, et al. Insulin, the insulin-like growth factor axis, and mortality in patients with nonmetastatic colorectal cancer. J Clin Oncol 2009;27:176–85.
35. Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Taylor SK, et al. Insulin- and obesity-related variables in early-stage breast cancer: correlations and time course of prognostic associations. J Clin Oncol 2012;30:164–71.
36. Slattery ML, Fitzpatrick FA. Convergence of hormones, inflammation, and energy-related factors: a novel pathway of cancer etiology. Cancer Prev Res 2009;2:922–30.
37. Moreschi C. Beziehungen zwischen ernährung und tumorwachstum. Z Immunitätsforsch Orig 1909;2:651–75.
38. Hursting SD, Lavigne JA, Berrigan D, Perkins SN, Barrett JC. Calorie restriction, aging, and cancer prevention: mechanisms of action and applicability to humans. Annu Rev Med 2003;54:131–52.
39. Tannenbaum A. The genesis and growth of tumors. II. Effects of caloric restriction per se. Cancer Res 1942;2:460–7.
40. Welsch MA, Cohen LA, Welsch CW. Inhibition of growth of human breast carcinoma xenografts by energy expenditure via voluntary

exercise in athymic mice fed a high-fat diet. Nutr Cancer 1995;23: 309–18.
41. Zheng X, Cui XX, Huang MT, Liu Y, Shih WJ, Lin Y, et al. Inhibitory effect of voluntary running wheel exercise on the growth of human pancreatic Panc-1 and prostate PC-3 xenograft tumors in immunodeficient mice. Oncol Rep 2008;19:1583–8.
42. Jones LW, Eves ND, Courneya KS, Chiu BK, Baracos VE, Hanson J, et al. Effects of exercise training on antitumor efficacy of doxorubicin in MDA-MB-231 breast cancer xenografts. Clin Cancer Res 2005;11:6695–8.
43. Colbert LH, Mai V, Perkins SN, Berrigan D, Lavigne JA, Wimbrow HH, et al. Exercise and intestinal polyp development in APCMin mice. Med Sci Sports Exerc 2003;35:1662–9.
44. Padovani M, Lavigne JA, Chandramouli GV, Perkins SN, Barrett JC, Hursting SD, et al. Distinct effects of calorie restriction and exercise on mammary gland gene expression in C57BL/6 mice. Cancer Prev Res 2009;2:1076–87.
45. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin 2012 Apr 26. [Epub ahead of print].
46. von Gruenigen VE, Tian C, Frasure H, Waggoner S, Keys H, Barakat RR. Treatment effects, disease recurrence, and survival in obese women with early endometrial carcinoma : a Gynecologic Oncology Group study. Cancer 2006;107:2786–91.
47. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625–38.
48. Giovannucci E, Liu Y, Platz EA, Stampfer MJ, Willett WC. Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. Int J Cancer 2007;121:1571–8.
49. Wright ME, Chang SC, Schatzkin A, Albanes D, Kipnis V, Mouw T, et al. Prospective study of adiposity and weight change in relation to prostate cancer incidence and mortality. Cancer 2007;109: 675–84.
50. Meyerhardt JA, Catalano PJ, Haller DG, Mayer RJ, Benson AB 3rd, Macdonald JS, et al. Influence of body mass index on outcomes and treatment-related toxicity in patients with colon carcinoma. Cancer 2003;98:484–95.
51. Meyerhardt JA, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, Nelson H, et al. Impact of body mass index and weight change after treatment on cancer recurrence and survival in patients with stage III colon cancer: findings from Cancer and Leukemia Group B 89803. J Clin Oncol 2008;26:4109–15.
52. Meyerhardt JA, Tepper JE, Niedzwiecki D, Hollis DR, McCollum AD, Brady D, et al. Impact of body mass index on outcomes and treatment-related toxicity in patients with stage II and III rectal cancer: findings from Intergroup Trial 0114. J Clin Oncol 2004;22:648–57.
53. Dignam JJ, Polite BN, Yothers G, Raich P, Colangelo L, O'Connell MJ, et al. Body mass index and outcomes in patients who receive adjuvant chemotherapy for colon cancer. J Natl Cancer Inst 2006;98:1647–54.
54. Shibakita M, Yoshimura H, Tachibana M, Ueda S, Nagasue N. Body mass index influences long-term outcome in patients with colorectal cancer. Hepatogastroenterology 2010;57:62–9.
55. Hines RB, Shanmugam C, Waterbor JW, McGwin G Jr, Funkhouser E, Coffey CS, et al. Effect of comorbidity and body mass index on the survival of African-American and Caucasian patients with colon cancer. Cancer 2009;115:5798–806.
56. Campbell PT, Newton CC, Dehal AN, Jacobs EJ, Patel AV, Gapstur SM. Impact of body mass index on survival after colorectal cancer diagnosis: the Cancer Prevention Study-II Nutrition Cohort. J Clin Oncol 2012;30:42–52.
57. Rock CL, Demark-Wahnefried W. Nutrition and survival after the diagnosis of breast cancer: a review of the evidence. J Clin Oncol 2002;20:3302–16.
58. Patterson RE, Cadmus LA, Emond JA, Pierce JP. Physical activity, diet, adiposity and female breast cancer prognosis: a review of the epidemiologic literature. Maturitas 2010;66:5–15.
59. Meyerhardt JA, Niedzwiecki D, Hollis D, Saltz LB, Hu FB, Mayer RJ, et al. Association of dietary patterns with cancer recurrence and survival in patients with stage III colon cancer. JAMA 2007;298: 754–64.
60. Berkow SE, Barnard ND, Saxe GA, Ankerberg-Nobis T. Diet and survival after prostate cancer diagnosis. Nutr Rev 2007;65:391–403.
61. Davies NJ, Batehup L, Thomas R. The role of diet and physical activity in breast, colorectal, and prostate cancer survivorship: a review of the literature. Br J Cancer 2011;105 Suppl 1:S52–73.
62. Meyerhardt JA, Ma J, Courneya KS. Energetics in colorectal and prostate cancer. J Clin Oncol 2010;28:4066–73.
63. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. JAMA 2005;293:2479–86.
64. Meyerhardt JA, Giovannucci EL, Holmes MD, Chan AT, Chan JA, Colditz GA, et al. Physical activity and survival after colorectal cancer diagnosis. J Clin Oncol 2006;24:3527–34.
65. Meyerhardt JA, Giovannucci EL, Ogino S, Kirkner GJ, Chan AT, Willett W, et al. Physical activity and male colorectal cancer survival. Arch Intern Med 2009;169:2102–8.
66. Kenfield SA, Stampfer MJ, Giovannucci E, Chan JM. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. J Clin Oncol 2011;29:726–32.
67. Richman EL, Kenfield SA, Stampfer MJ, Paciorek A, Carroll PR, Chan JM. Physical activity after diagnosis and risk of prostate cancer progression: data from the cancer of the prostate strategic urologic research endeavor. Cancer Res 2011;71:3889–95.
68. Chen X, Lu W, Zheng W, Gu K, Matthews CE, Chen Z, et al. Exercise after diagnosis of breast cancer in association with survival. Cancer Prev Res 2011;4:1409–18.
69. Holick CN, Newcomb PA, Trentham-Dietz A, Titus-Ernstoff L, Bersch AJ, Stampfer MJ, et al. Physical activity and survival after diagnosis of invasive breast cancer. Cancer Epidemiol Biomarkers Prev 2008;17:379–86.
70. Irwin ML, Smith AW, McTiernan A, Ballard-Barbash R, Cronin K, Gilliland FD, et al. Influence of pre- and postdiagnosis physical activity on mortality in breast cancer survivors: the health, eating, activity, and lifestyle study. J Clin Oncol 2008;26:3958–64.
71. Pierce JP, Stefanick ML, Flatt SW, Natarajan L, Sternfeld B, Madlensky L, et al. Greater survival after breast cancer in physically active women with high vegetable-fruit intake regardless of obesity. J Clin Oncol 2007;25:2345–51.
72. Sternfeld B, Weltzien E, Quesenberry CP Jr, Castillo AL, Kwan M, Slattery ML, et al. Physical activity and risk of recurrence and mortality in breast cancer survivors: findings from the LACE study. Cancer Epidemiol Biomarkers Prev 2009;18:87–95.
73. Irwin ML, McTiernan A, Manson JE, Thomson CA, Sternfeld B, Stefanick ML, et al. Physical activity and survival in postmenopausal women with breast cancer: results from the women's health initiative. Cancer Prev Res 2011;4:522–9.
74. Meyerhardt JA, Heseltine D, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. J Clin Oncol 2006;24:3535–41.
75. Irwin ML, Varma K, Alvarez-Reeves M, Cadmus L, Wiley A, Chung GG, et al. Randomized controlled trial of aerobic exercise on insulin and insulin-like growth factors in breast cancer survivors: the Yale Exercise and Survivorship study. Cancer Epidemiol Biomarkers Prev 2009;18:306–13.
76. Ligibel JA, Campbell N, Partridge A, Chen WY, Salinardi T, Chen H, et al. Impact of a mixed strength and endurance exercise intervention on insulin levels in breast cancer survivors. J Clin Oncol 2008;26: 907–12.
77. Blanchard CM, Courneya KS, Stein K. Cancer survivors' adherence to lifestyle behavior recommendations and associations with health-related quality of life: results from the American Cancer Society's SCS-II. J Clin Oncol 2008;26:2198–204.
78. Griggs JJ, Culakova E, Sorbero ME, van Ryn M, Poniewierski MS, Wolff DA, et al. Effect of patient socioeconomic status and body mass

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index on the quality of breast cancer adjuvant chemotherapy. J Clin Oncol 2007;25:277–84.
79. Klabunde CN, Legler JM, Warren JL, Baldwin LM, Schrag D. A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. Ann Epidemiol 2007;17:584–90.
80. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Dercksen MW, Coebergh JW, Haak HR. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. Int J Cancer 2007;120:1986–92.
81. Peairs KS, Barone BB, Snyder CF, Yeh HC, Stein KB, Derr RL, et al. Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. J Clin Oncol 2011;29:40–6.
82. Goodwin PJ, Stambolic V, Lemieux J, Chen BE, Parulekar WR, Gelmon KA, et al. Evaluation of metformin in early breast cancer: a modification of the traditional paradigm for clinical testing of anti-cancer agents. Breast Cancer Res Treat 2011;126:215–20.
83. Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960–1994. Int J Obes Relat Metab Disord 1998;22:39–47.
84. The practical guide: Identification, evaluation, and treatment of overweight and obesity in adults: National Institutes of Health; 2000.
85. U.S. Preventive Services Taskforce. Screening for obesity in adults: recommendations and rationale. Ann Intern Med 2003;139:930–2.
86. Leblanc ES, O'Connor E, Whitlock EP, Patnode CD, Kapka T. Effectiveness of primary care-relevant treatments for obesity in adults: a systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med 2011;155:434–47.
87. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009;360:859–73.
88. Foster GD, Wyatt HR, Hill JO, Makris AP, Rosenbaum DL, Brill C, et al. Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: a randomized trial. Ann Intern Med 2010;153:147–57.
89. Wadden TA, Webb VL, Moran CH, Bailer BA. Lifestyle modification for obesity: new developments in diet, physical activity, and behavior therapy. Circulation 2012;125:1157–70.
90. Kushi LH, Byers T, Doyle C, Bandera EV, McCullough M, McTiernan A, et al. American Cancer Society guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin 2006;56:254–81; quiz 313–4.
91. Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW, Smith BK. American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. Med Sci Sports Exerc 2009;41:459–71.
92. Perri MG, McAllister DA, Gange JJ, Jordan RC, McAdoo G, Nezu AM. Effects of four maintenance programs on the long-term management of obesity. J Consult Clin Psychol 1988;56:529–34.
93. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403.
94. Ryan DH, Espeland MA, Foster GD, Haffner SM, Hubbard VS, Johnson KC, et al. Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. Control Clin Trials 2003;24:610–28.
95. Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, Clark JM, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care 2007;30:1374–83.
96. Appel LJ, Clark JM, Yeh HC, Wang NY, Coughlin JW, Daumit G, et al. Comparative effectiveness of weight-loss interventions in clinical practice. N Engl J Med 2011;365:1959–68.
97. Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. Arch Intern Med 2010;170:1566–75.
98. Kaplan LM. Pharmacological therapies for obesity. Gastroenterol Clin North Am 2005;34:91–104.
99. Hollander PA, Elbein SC, Hirsch IB, Kelley D, McGill J, Taylor T, et al. Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. Diabetes Care 1998;21:1288–94.
100. Li Z, Maglione M, Tu W, Mojica W, Arterburn D, Shugarman LR, et al. Meta-analysis: pharmacologic treatment of obesity. Ann Intern Med 2005;142:532–46.
101. Sjostrom L, Narbro K, Sjostrom CD, Karason K, Larsson B, Wedel H, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med 2007;357:741–52.
102. Wadden TA, Berkowitz RI, Womble LG, Sarwer DB, Phelan S, Cato RK, et al. Randomized trial of lifestyle modification and pharmacotherapy for obesity. N Engl J Med 2005;353:2111–20.
103. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, et al. Long-term mortality after gastric bypass surgery. N Engl J Med 2007;357:753–61.
104. Smith BR, Schauer P, Nguyen NT. Surgical approaches to the treatment of obesity: bariatric surgery. Endocrinol Metab Clin North Am 2008;37:943–64.
105. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999–2008. JAMA 2010;303:235–41.
106. Santry HP, Gillen DL, Lauderdale DS. Trends in bariatric surgical procedures. JAMA 2005;294:1909–17.
107. Flum DR, Belle SH, King WC, Wahed AS, Berk P, Chapman W, et al. Perioperative safety in the longitudinal assessment of bariatric surgery. N Engl J Med 2009;361:445–54.
108. Ashrafian H, Ahmed K, Rowland SP, Patel VM, Gooderham NJ, Holmes E, et al. Metabolic surgery and cancer: protective effects of bariatric procedures. Cancer 2011;117:1788–99.
109. Sjostrom L, Gummesson A, Sjostrom CD, Narbro K, Peltonen M, Wedel H, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. Lancet Oncol 2009;10:653–62.
110. Shade ED, Ulrich CM, Wener MH, Wood B, Yasui Y, Lacroix K, et al. Frequent intentional weight loss is associated with lower natural killer cell cytotoxicity in postmenopausal women: possible long-term immune effects. J Am Diet Assoc 2004;104:903–12.
111. Denlinger CS, Barsevick AM. The challenges of colorectal cancer survivorship. J Natl Compr Canc Netw 2009;7:883–93; quiz 94.
112. Harrington CB, Hansen JA, Moskowitz M, Todd BL, Feuerstein M. It's not over when it's over: long-term symptoms in cancer survivors–a systematic review. Int J Psychiatry Med 2010;40:163–81.
113. Shi Q, Smith TG, Michonski JD, Stein KD, Kaw C, Cleeland CS. Symptom burden in cancer survivors 1 year after diagnosis: a report from the American Cancer Society's Studies of Cancer Survivors. Cancer 2011;117:2779–90.
114. Ashing-Giwa KT, Padilla G, Tejero J, Kraemer J, Wright K, Coscarelli A, et al. Understanding the breast cancer experience of women: a qualitative study of African American, Asian American, Latina and Caucasian cancer survivors. Psychooncology 2004;13:408–28.
115. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010;42:1409–26.
116. Zabora J, BrintzenhofeSzoc K, Curbow B, Hooker C, Piantadosi S. The prevalence of psychological distress by cancer site. Psychooncology 2001;10:19–28.
117. Demark-Wahnefried W, Bowen DJ, Jabson JM, Paskett ED. Scientific bias arising from sampling, selective recruitment, and attrition: the case for improved reporting. Cancer Epidemiol Biomarkers Prev 2011;20:415–8.
118. Physical Activity Guidelines Advisory Committee report, 2008. To the Secretary of Health and Human Services. Part A: executive summary. Nutr Rev 2009;67:114–20.
119. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. J Cancer Surviv 2010;4:87–100.

120. Brown JC, Huedo-Medina TB, Pescatello LS, Pescatello SM, Ferrer RA, Johnson BT. Efficacy of exercise interventions in modulating cancer-related fatigue among adult cancer survivors: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2011;20:123–33.

121. Craft LL, Vaniterson EH, Helenowski IB, Rademaker AW, Courneya KS. Exercise effects on depressive symptoms in cancer survivors: a aystematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2012;21:3–19.

122. Ferrer RA, Huedo-Medina TB, Johnson BT, Ryan S, Pescatello LS. Exercise interventions for cancer survivors: a meta-analysis of quality of life outcomes. Ann Behav Med 2011;41:32–47.

123. Courneya KS, Booth CM, Gill S, O'Brien P, Vardy J, Friedenreich CM, et al. The colon health and life-long exercise change trial: a randomized trial of the National Cancer Institute of Canada Clinical Trials Group. Curr Oncol 2008;15:279–85.

124. Chlebowski RT, Blackburn GL, Thomson CA, Nixon DW, Shapiro A, Hoy MK, et al. Dietary fat reduction and breast cancer outcome: interim efficacy results from the Women's Intervention Nutrition Study. J Natl Cancer Inst 2006;98:1767–76.

125. Pierce JP, Natarajan L, Caan BJ, Parker BA, Greenberg ER, Flatt SW, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. JAMA 2007;298:289–98.

126. Demark-Wahnefried W, Clipp EC, Lipkus IM, Lobach D, Snyder DC, Sloane R, et al. Main outcomes of the FRESH START trial: a sequentially tailored, diet and exercise mailed print intervention among breast and prostate cancer survivors. J Clin Oncol 2007;25:2709–18.

127. Demark-Wahnefried W, Case LD, Blackwell K, Marcom PK, Kraus W, Aziz N, et al. Results of a diet/exercise feasibility trial to prevent adverse body composition change in breast cancer patients on adjuvant chemotherapy. Clin Breast Cancer 2008;8:70–9.

128. Loprinzi CL, Athmann LM, Kardinal CG, O'Fallon JR, See JA, Bruce BK, et al. Randomized trial of dietician counseling to try to prevent weight gain associated with breast cancer adjuvant chemotherapy. Oncology 1996;53:228–32.

129. Djuric Z, Ellsworth JS, Weldon AL, Ren J, Richardson CR, Resnicow K, et al. A diet and exercise intervention during chemotherapy for breast cancer. Open Obes J 2011;3:87–97.

130. de Waard F, Ramlau R, Mulders Y, de Vries T, van Waveren S. A feasibility study on weight reduction in obese postmenopausal breast cancer patients. Eur J Cancer Prev 1993;2:233–8.

131. Djuric Z, DiLaura NM, Jenkins I, Darga L, Jen CK, Mood D, et al. Combining weight-loss counseling with the weight watchers plan for obese breast cancer survivors. Obes Res 2002;10:657–65.

132. Mefferd K, Nichols JF, Pakiz B, Rock CL. A cognitive behavioral therapy intervention to promote weight loss improves body composition and blood lipid profiles among overweight breast cancer survivors. Breast Cancer Res Treat 2007;104:145–52.

133. Morey MC, Snyder DC, Sloane R, Cohen HJ, Peterson B, Hartman TJ, et al. Effects of home-based diet and exercise on functional outcomes among older, overweight long-term cancer survivors: RENEW: a randomized controlled trial. JAMA 2009;301:1883–91.

134. Ontario Clinical Oncology Group (OCOG). Lifestyle intervention study in adjuvant treatment of early breast cancer (LISA). Available from: http://clinicaltrials.gov/ct2/show/NCT00463489. [cited June 2012].

135. Taylor DL, Nichols JF, Pakiz B, Bardwell WA, Flatt SW, Rock CL. Relationships between cardiorespiratory fitness, physical activity, and psychosocial variables in overweight and obese breast cancer survivors. Int J Behav Med 2010;17:264–70.

136. Demark-Wahnefried W, Morey MC, Sloane R, Snyder DC, Miller PE, Hartman TJ, et al. Reach out to enhance wellness home-based diet-exercise intervention promotes reproducible and sustainable long-term improvements in health behaviors, body weight, and physical functioning in older, overweight/obese cancer survivors. J Clin Oncol 2012 May 21. [Epub ahead of print].

137. Pal SK, Hurria A. Impact of age, sex, and comorbidity on cancer therapy and disease progression. J Clin Oncol 2010;28:4086–93.

138. Yabroff KR, Lawrence WF, Clauser S, Davis WW, Brown ML. Burden of illness in cancer survivors: findings from a population-based national sample. J Natl Cancer Inst 2004;96:1322–30.

139. Schmitz KH, Ahmed RL, Troxel A, Cheville A, Smith R, Lewis-Grant L, et al. Weight lifting in women with breast-cancer-related lymphedema. N Engl J Med 2009;361:664–73.

140. Gortmaker SL, Swinburn BA, Levy D, Carter R, Mabry PL, Finegood DT, et al. Changing the future of obesity: science, policy, and action. Lancet 2011;378:838–47.

141. Sacks G, Swinburn B, Lawrence M. Obesity policy action framework and analysis grids for a comprehensive policy approach to reducing obesity. Obes Rev 2009;10:76–86.

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