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The Role of Obesity in Cancer Survival and Recurrence

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Abstract

Obesity and components of energy imbalance, i.e., 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: 1) mechanisms associated with obesity and energy balance that influence cancer progression; 2) complexities of

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studying and interpreting energy balance in relation to cancer recurrence and survival; 3) associations between obesity and cancer risk, recurrence, and mortality; 4) interventions that promote weight loss, increased physical activity, and negative energy balance as a means of cancer control; and 5) future directions.

Keywords

neoplasms; obesity; diet; physical activity; survival; recurrence

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 which he termed “karkinos,” warned of the dangers of too much food and too little exercise (1). Almost two 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 regarding 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/m²) and 500 million are obese (BMI 30kg/m²) (10). Also, with the earlier onset of overweight and obesity often occurring during childhood, there is considerable concern, since 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: 1) mechanisms associated with obesity and energy balance that influence cancer progression; 2) complexities of studying and interpreting energy balance in relation to cancer recurrence and survival; 3) associations between obesity and cancer risk, recurrence, and mortality; 4) interventions that promote weight loss and negative energy balance as a means of cancer control; and 5) 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 appears 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 is comprised of three components: 1) resting metabolic rate (RMR), the energy required for normal body processes, which accounts for the majority of energy needs; 2)

thermic effect of food, the relatively minor amount of energy needed to digest and metabolize food; and 3) 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 since lean body mass determines RMR. This relationship is worth noting since 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) (crosstalk with epidermal growth factor), phosphatidylinositol 3-kinase, and AMP-activated protein kinase, and many other entities. Components of insulin resistance syndrome (IRS) have been well-studied in both breast (19–23) and colorectal cancer (24–31). For example, in non-diabetic 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 (IR α) on breast cancer cells, provides a biologic basis for this effect, since 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), IL1 β , and tumor necrosis factor- α (TNF α) that lead to the activation of nuclear factor-kappa B (NF κ B) and downstream effects that signal through the mammalian target of rapamycin (mTOR) to initiate transcription. This cascade also appears influenced by sex hormones (estradiol and testosterone) and growth factors, notably vascular endothelial growth factor (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, 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 (see *Cancer Prevention XX:XXX–XXX*, 2012).

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 to 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, two (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. Though not in a cancer model, Padovani et al. (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 three genes. Thus, at least in animal models, the biological 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, 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, since 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 over 40 studies of women diagnosed with breast cancer, Protani et al. (7) reported a modest, but statistically significant and clinically-relevant increase in all-cause and breast cancer specific mortality in obese versus non-obese women (HR[95% CI]: 1.33[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 prior to 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 non-metastatic colorectal cancer show poorer outcomes solely in extremely obese patients, i.e., BMI ≥ 35 kg/m² (8, 50–55). In a cohort of ~4,000 stage II-III colon cancer patients participating in four NCI-sponsored adjuvant therapy trials, BMI ≥ 35 kg/m² 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 post-diagnosis or post-diagnosis BMI on cancer recurrence and survival and neither found an association (51, 56), with the more recent study by Campbell et al. suggesting that obesity pre-diagnosis is most important.

To date, no observational studies assessed energy intake using validated methods, though several have evaluated associations between dietary factors and cancer 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 macro-nutrients, 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 seven studies suggest that women who participate in modest levels of physical activity postdiagnosis have significantly better outcomes as compared to sedentary women. For example, women who engage in >9 MET-hours/week of physical activity (equivalent to walking at an average pace for 3 hours/week) 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/week) (63). Similar findings have been reported in colorectal cancer survivors, in whom participation in ≥ 18 MET-hours/week of post-diagnosis 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 minutes/week and reductions of 61% and 49% were seen respectively in prostate-specific and all-cause mortality in men who engaged in ≥ 3 hours/week 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 since 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 LifeLong 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 demonstrating that obese breast cancer patients receive less adequate doses of chemotherapeutic agents, treatment stands as an important confounder or effect modifier (78). While 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 co-morbidities, which are highly prevalent among cancer patients since 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 5–17% of individuals with breast, colon or prostate cancer (79). Here, the risk of death may be 2 to 3 fold higher compared to 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, e.g., 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 methodological 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 US 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 7–10%, which has been shown to improve several obesity-related conditions, such as diabetes mellitus and risk of cardiovascular disease (CVD) (84). The US 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 500–1000 kcal/day (sufficient to induce a 1–2 pound/week 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 minutes/week of brisk walking) are necessary to maintain lost weight (89, 91, 92). The Diabetes Prevention Program (DPP) (93) and the Look AHEAD study (94, 95) are two of the largest lifestyle modification weight loss trials. The DPP randomized 3234 obese adults with impaired glucose tolerance to usual care, metformin, or a lifestyle intervention. Lifestyle intervention participants were instructed to

(i) reduce their energy intake by 500–1000 kcal/day (by decreasing portion sizes, fat, and sugar), (ii) increase fruit and vegetable intake, and (iii) exercise for >150 minutes/week (96). They kept records of their weight, food intake, and physical activity, which they reviewed regularly with dietitians. The study demonstrated 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/m² (or >27 kg/m² with comorbid conditions) (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 14–26%, 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, i.e., 5.1% of the U.S. population with a BMI>40 kg/m² (84, 105), as well as attendant risks, e.g., mortality rates of 0.1–0.3% and complication rates of 4–9% (106, 107). Of particular interest in the context of this review, a diagnosis of cancer within the past five 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 to 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 hazard ratios 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 post-diagnosis 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 post-treatment 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 in order to assure adequate immune function; moreover, risks for infection in gym-based programs must be considered (110). Another consideration is chemotherapy-induced sarcopenia which can be exacerbated by rapid weight loss (exceeding 2 pounds/week) via regimens that are focused solely on diet (13) –

thus reinforcing the need for multi-component 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 demonstrated 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, musculo-skeletal injuries and cardiac risk are minimized (115). Additionally, some patients will experience psychological distress (116), e.g., 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 demonstrated. 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.

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 non-respondents, 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 socio-economic 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 demonstrated 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), 30 minutes/session (121), and delivered after completion of primary curative treatment (119).

Based on 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 2–6 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) (124) and the Women's Healthy Eating and Lifestyle (WHEL) (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=2437, 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 weight) compared to 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=3088, enrolled up to 4 years post diagnosis), used telephone-based dietary counseling to promote a daily intake of five vegetable servings plus 16 ounces of vegetable juice or equivalent, three fruit servings, 30 g fiber, and 15–20% 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% versus 16.9%) or survival (10.1% versus 10.3%). While the high fruit and vegetable intake of WHEL participants at baseline may have undermined the trial's ability to detect between-arm differences, the differential in weight change observed between the two trials also may have contributed to the discrepant findings.

Similar to WINS, other dietary interventions resulted in modest (2–3% of initial body weight) yet significant weight loss as a consequence of lower fat, high fruit and vegetable diets, e.g., the FRESH START trial conducted in 543 newly-diagnosed breast and prostate cancer survivors (126). Additionally, 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 six 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), while 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 et al. 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, i.e., the Healthy Weight Management (HWM) Study (n=85) (132), and the Survivors Health And Physical Exercise (SHAPE) trial (n=258) (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 LDL

cholesterol. While 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 post-diagnosis) 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/week) 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 to 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 two current trials. The Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) trial is a multi-site 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 2500 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 demonstrate 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 over age 60 and come to the diagnosis with co-morbid 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.

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, and improved diet, and increased physical activity. Physical training has been shown to be effective for breast cancer patients with lymphedema (139), while obesity has been shown to exacerbate this condition. Thus, there may be many additional reasons for considering weight maintenance/loss programs for survivors.

Currently, we have limited evidence regarding 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, cardiovascular disease) should be an important goal in cancer survivors.

Future directions

Despite the significant gain in knowledge regarding 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 trans-disciplinary 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 Figure 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.

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Energy Balance

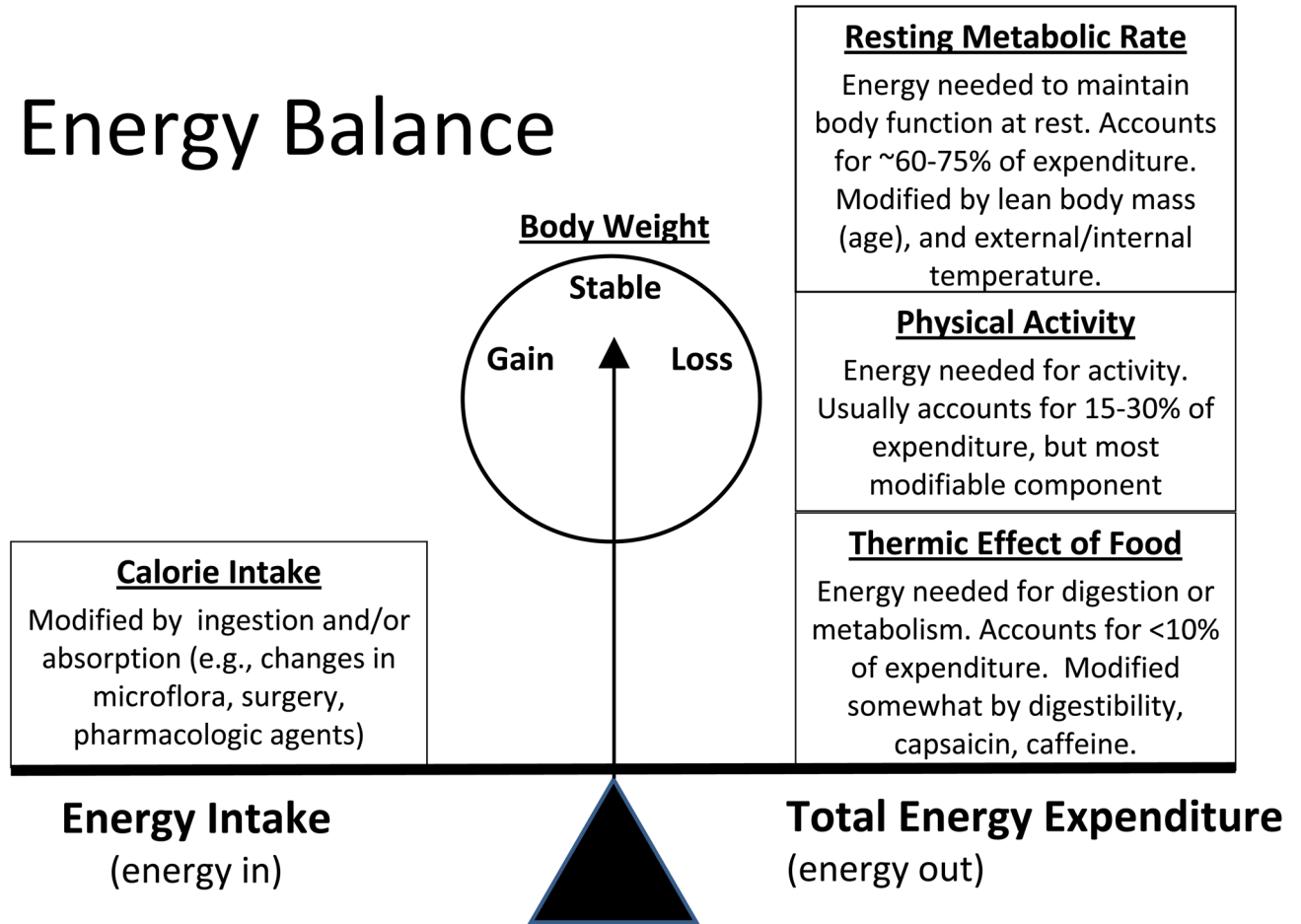


Figure 1.

The Complex Dynamic Nature of Energy Balance: Energy balance occurs when energy intake (measured in kilocalories) equals total energy expenditure (resting metabolic rate + 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.

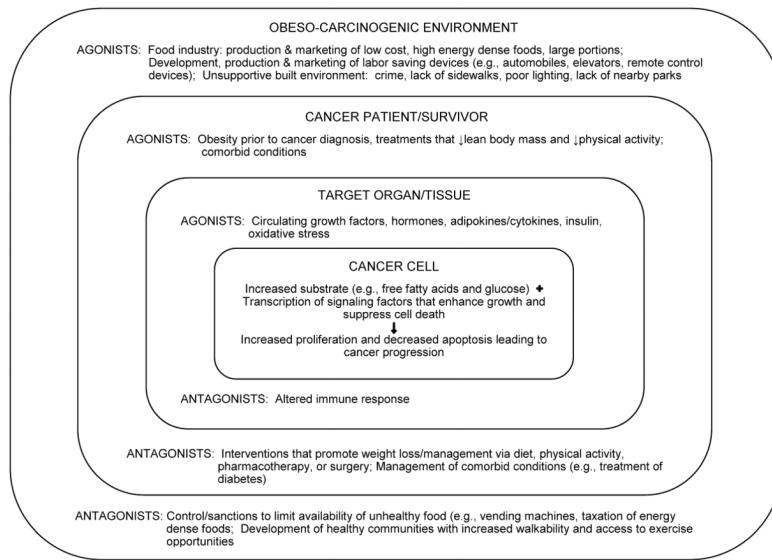


Figure 2. Cancer progression ultimately is a product of the larger environment. High energy dense foods are foods high in energy (calories) per gram weight, e.g., fried foods (high in fat) whereas fruits and vegetables are low energy dense foods.

Table 1

Summary of the evidence and evidence gaps regarding research on energy balance and cancer recurrence and survival

EVIDENCE	EVIDENCE GAPS
<p style="text-align: center;">Energy Balance and Cancer Risk</p> <ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • 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?
<p style="text-align: center;">Energy Balance and Cancer Recurrence and Promotion</p> <ul style="list-style-type: none"> • Obesity at diagnosis is a poor prognostic factor for cancers of the breast, colon and prostate. 	<ul style="list-style-type: none"> • 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 clinico-pathological factors, such as later stage at diagnosis, reduced treatment efficacy, or contribution of co-morbid factors (e.g., diabetes) to affect disease-specific and overall outcomes? • What is the impact of weight change during various stages of neoplasia, e.g., preneoplastic lesions, early stage non-aggressive 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?
<p style="text-align: center;">Mechanisms of Energy Balance and Cancer Promotion</p>	

EVIDENCE	EVIDENCE GAPS
<ul style="list-style-type: none"> • 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. • Obesity-associated metabolic syndrome is associated with some forms of cancer, e.g., breast cancer, and may support the use of energy-related mimetics, such as metformin, as adjunctive treatment. 	<ul style="list-style-type: none"> • 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? • Are there additional, yet not well described, effects on molecular pathways, e.g., 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?
<ul style="list-style-type: none"> • Varying levels of evidence exist regarding the role of energy balance (and each of its separate components) on cancer incidence and outcomes. <ul style="list-style-type: none"> – 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. 	<p style="text-align: center;">Energy Intake and Physical Activity and their Comparative Effects on Cancer</p> <ul style="list-style-type: none"> • 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?
<ul style="list-style-type: none"> • Much is known regarding weight loss in healthy populations. <ul style="list-style-type: none"> – 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 pre-portioned, 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 appears most beneficial in improving body composition. 	<p style="text-align: center;">Weight Loss Interventions and their Applications among Cancer Survivors</p> <ul style="list-style-type: none"> • What is the effect of weight loss and long-term weight control on cancer outcomes? What are potential moderators (i.e., treatments, others medications, etc.)? • 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?

EVIDENCE	EVIDENCE GAPS
<ul style="list-style-type: none"> • 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) appear important, as 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. 	<ul style="list-style-type: none"> • Are there other causes of treatment-related weight gain among cancer patients, e.g., 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 regarding the dissemination of weight loss interventions: <ul style="list-style-type: none"> - Which cancer survivors should receive them? - Who will deliver them? - Who will pay for them?

Table 2

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

<ul style="list-style-type: none"> • Determination of the optimal cancer outcome to evaluate, e.g., recurrence, progression to metastases, or cancer death. The decision rests on the following factors: <ul style="list-style-type: none"> – 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
<ul style="list-style-type: none"> • Inclusion of a comparison group to account for social interaction/placebo effects, which may be particularly important for trials targeting patient-reported outcomes.
<ul style="list-style-type: none"> • Control for confounding by pathologic characteristics (e.g., cancer stage, 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.
<ul style="list-style-type: none"> • Control for confounding or effect modification for factors that may co-occur with obesity, e.g., physical activity, energy intake, diabetes and other comorbid conditions, and smoking
<ul style="list-style-type: none"> • Knowledge that treatment and management of cancer might affect the interpretation of the results if: <ul style="list-style-type: none"> – the presentation or selection of treatment options varies by weight status – the treatment success varies by weight status, e.g., whether the chance of positive surgical margins and thus recurrence varies by weight status – potential for reverse causation as some treatments, e.g., hormonal therapy, can lead to an increase in body fat accumulation, especially centrally, and metabolic perturbations
<ul style="list-style-type: none"> • Recognition that the effects of energy balance on cancer may differ depending on: <ul style="list-style-type: none"> – Cancer type and stage – Treatment – Race/ethnicity of the host – Body fat distribution – Other co-factors (e.g., smoking, co-morbidity, medications) – Awareness that findings of studies conducted in non-Hispanic white survivors of non-metastatic 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.
<ul style="list-style-type: none"> • Awareness that the effects of adiposity on cancer may differ depending on: <ul style="list-style-type: none"> – Body fat distribution and extent of body fatness – Volitional vs. non-volitional weight loss – Rapid vs. slower weight change – Intermittent vs. continual exposure
<ul style="list-style-type: none"> • Realization that the effects of negative energy balance on cancer may differ depending on:

<ul style="list-style-type: none"> - Diet composition - Type of physical activity - The magnitude of energy deficit
<ul style="list-style-type: none"> • Awareness that the measurement of diet and physical activity is difficult, and discrepancies in methods pose a challenge for pooling of data or performing meta-analyses.
<ul style="list-style-type: none"> • Consideration of the relationships between obesity, comorbidity, and treatment (which may or may not be independent) in the analysis and interpretation of results.
<ul style="list-style-type: none"> • Consideration within the study design and analysis to reduce and account for potential measurement error (e.g., energy intake, physical activity, obesity).
<ul style="list-style-type: none"> • Lack of control for all components of energy balance (i.e., both energy intake and physical activity, as well as BMI).
<ul style="list-style-type: none"> • Lack of characterization of the study population regarding accrual (enrollees vs. larger pool of cancer survivors) and attrition (completers vs. dropouts).
<ul style="list-style-type: none"> • Adherence and long-term change in behavior.
<ul style="list-style-type: none"> • Adequate power to detect significant associations.

Table 3

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

Administrative:	
<ul style="list-style-type: none"> Expand grant review panel capacity to reflect scientific expertise to adequately review current research issues in cancer survivors, including biological and behavioral dynamics, such as the impact of energy balance. 	
<ul style="list-style-type: none"> Strengthen resources to share innovative measures and methodologies to foster cutting-edge science. 	
<ul style="list-style-type: none"> 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. 	
<ul style="list-style-type: none"> Establish a better understanding of cost-effectiveness of approaches. Increase research on economic questions as they relate to obesity and cancer. 	
<ul style="list-style-type: none"> 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:	
<ul style="list-style-type: none"> 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, electronic momentary assessment (EMA) technology and physical activity (accelerometry, ACT24, EMA technology). 	
<ul style="list-style-type: none"> Collect additional data pertinent to the evaluation of energy balance and cancer outcomes: <ul style="list-style-type: none"> Weight (adiposity) status Biological samples (tumor and normal tissue, blood, urine, buccal cells, etc.) Comorbid conditions Complete cancer treatment data Complete data on medication-use (including over-the-counter) 	
<ul style="list-style-type: none"> Determine if there are differences in the association of obesity/weight gain with cancer outcomes in cancer patients by timing relative to cancer diagnosis and treatment (pre-diagnosis, at diagnosis/treatment, in the months and years following diagnosis/treatment, or over the life course). 	
<ul style="list-style-type: none"> 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. 	
<ul style="list-style-type: none"> Expand translational research with an emphasis on cancer survivors. 	
<ul style="list-style-type: none"> Promote a transdisciplinary research focus that engages expertise from basic laboratory, clinical, environmental, public health and community expertise. 	
<ul style="list-style-type: none"> Integrate individual and social-environmental approaches to explain and modify energy-balance related health behaviors and cancer survivorship. 	

<ul style="list-style-type: none"> • 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 in order to help strengthen the capacity of programs and policies to have maximum reach and impact.
<p>Pharmacologic Trials:</p> <ul style="list-style-type: none"> • Capture BMI (as well as other measures of adiposity and components of energy balance, e.g., dietary intake and physical activity) within pharmacologic RCTs to analyze the impact of weight status, either synergistically or independently, on survival endpoints. • Collect biological 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.
<p>Mechanistic Studies:</p> <ul style="list-style-type: none"> • Identify and validate biomarkers for cancer recurrence and death. • Determine the biological mechanisms that regulate energy balance and inform the development of more effective lifestyle interventions that better reflect the biological influence of human behavior.