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OBESITY IN CANCER SURVIVAL

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Abstract

Although obesity is a well known risk factor for several cancers, its role on cancer survival is poorly understood. We conducted a systematic literature review to assess the current evidence evaluating the impact of body adiposity on the prognosis of the three most common obesity-related cancers: prostate, colorectal, and breast. We included 33 studies of breast cancer, six studies of prostate cancer, and eight studies of colorectal cancer. We note that the evidence over-represents breast cancer survivorship research and is sparse for prostate and colorectal cancers. Overall, most studies support a relationship between body adiposity and site-specific mortality or cancer progression. However, most of the research was not specifically designed to study these outcomes and, therefore, several methodological issues should be considered before integrating their results to draw conclusions. Further research is urgently warranted to assess the long-term impact of obesity among the growing population of cancer survivors.

Keywords

BMI; adiposity; cancer prognosis; breast cancer; colorectal cancer; prostate cancer

INTRODUCTION

Cancer survivors are defined as individuals with a cancer diagnosis regardless of the course of the illness, until the end of their life (89). The number of cancer survivors is steadily on the rise. The National Cancer Institute estimated that there were approximately 12 million cancer survivors in 2008 (1). The significant rise in cancer survivors in the past four decades may be partially attributed to longer survival and population aging (78) since age is the single most important risk factor for cancer. Furthermore, early detection of cancer, and better treatment (91) as well as reduction in disease-specific mortality (101) may also contribute to the rapidly-growing population of cancer survivors. It is projected that the number of cancer survivors over the age of 65 years will increase by 42% in the year 2020 (78).

The American Cancer Society (ACS) recently reported that the 5-year relative survival rate for all cancers combined is 66% (2). Cancer survivors are at risk of adverse cancer outcomes including disease recurrence and death. In fact, cancer mortality is the leading cause of death

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among persons younger than 85 years of age, surpassing deaths related to cardiovascular disease (101). Additionally, a large proportion of healthcare dollars are spent on cancer. The financial burden for prostate, breast and colorectal cancers after diagnosis was in the proximity of \$50 billion in 2010 (112). The surge in the number of cancer survivors coupled with the large economic burden makes it important to identify modifiable risk factors that may prevent progression, recurrence and cancer mortality after detection of cancer.

An important risk factor to consider among cancer survivors is obesity. A comprehensive systematic review of the evidence by the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) concluded that body fatness is an established risk factor for several cancers (108). The prevalence of cancer has increased in parallel to obesity, a phenomenon that has reached epidemic proportions in the United States (35). It was estimated that over 50% of all cancers detected are in sites in which obesity was implicated (101). Obesity has been shown to be associated with increased cancer mortality (11), poor quality of life including physical functioning and an inadequate response to cancer treatment among cancer patients (5; 73).

Potential mechanisms linking body adiposity to cancer progression and mortality

There is growing evidence linking a number of obesity-related mechanisms to carcinogenesis, and emerging experimental findings also point to a role in cancer progression and/or response to treatment. In particular, adipocyte-derived cytokines and inflammatory factors, and obesity-related hormonal disturbances have been postulated to play major roles (43). These pathways are described below and delineated in Figure 1.

Insulin and Insulin-Like Growth Factor axis—A salient underlying biologic mechanism via which obesity may influence cancer progression and cancer-specific mortality is through perturbations in the insulin and insulin-like growth factor (IGF-1) axis. Higher concentrations of insulin are hypothesized to stimulate cell proliferation through increased production of bioavailable IGF-1 (88) by activating target genes downstream of the insulin receptor, which comprise a signaling network that dictates cell growth, survival and proliferation (67; 90).

Aberrations in the insulin-IGF-1 axis may stimulate the production of adipocyte-derived vascular endothelial growth factor (VEGF), a critical angiogenic factor that supports cell survival and migration (40). Furthermore, blood insulin-IGF-1 concentrations are a major determinant of circulating levels of sex steroid (described below) (48).

Adipokines—Recent research has established that the fat tissue is an “endocrine organ”, which produces and secretes polypeptide hormones (approximately 50 known hormones), collectively known as adipokines, hypothesized to influence cancer pathophysiology (33). Leptin and adiponectin are the two most abundant adipokines produced by adipocytes and are hypothesized to play a role in tumor development and progression.

Leptin: Leptin, which is intrinsically related to adiposity, is the key player in energy balance and appetite control (83). In lean persons, leptin signals appetite reduction to the brain. However, in persons with increased adiposity, there is overproduction of leptin causing ‘leptin resistance’ in the brain. Leptin induces expression of VEGF, which is responsible for cancer progression via its potent pro-angiogenic effect (40) and has been shown to induce cell migration and expression of growth factors in human prostate and endometrial cancer cells *in vitro* (36) (99). Furthermore, leptin, which is tightly associated with insulin metabolism, interferes with insulin signaling, creating conditions conducive to cell growth (34).

Adiponectin: Contrary to leptin, adiponectin, secreted most abundantly from abdominal fat, is inversely associated with body fatness, hyperinsulinemia and inflammation (33). Adiponectin is an important insulin sensitizing agent and is hypothesized to oppose cell proliferation and inhibit cell growth and migration (4). Evidence also suggests an anti-angiogenic potential for adiponectin (4). However, it is not clear whether adiponectin is linked to cancer pathogenesis through its independent effect on tumors, or indirectly through insulin-dictated pathways.

Inflammation: Body adiposity is associated with higher levels of proinflammatory cytokines (15) including prostaglandin E₂, tumor necrosis factor (TNF)- α , interleukin (IL)-6, IL-8, IL-10, macrophage inflammatory protein-1, and monocyte chemoattractant protein-1 (32; 33). These factors cumulatively produce an environment conducive to survival and growth of cancer cells. Furthermore, TNF- α and IL-6 are known to stimulate VEGF production (88). A possible mechanism through which inflammatory markers realize their mitogenic potential is the activation of nuclear factor kappa B (NF- κ B), a transcription factor present in the cytoplasmic fluid of cells. NF- κ B may also be activated by insulin to enhance gene activation and ultimately cell growth and survival. Epidemiologic studies support that adipocyte-derived cytokines modulate growth of cancer cells (15; 54; 105; 113).

Steroid hormones—Obesity-associated imbalances of steroid hormones including estrogen, progesterone, androgens and adrenal steroids may contribute to the survival, growth and ultimately progression of male and female cancers (44). Body adiposity augments the level of the aromatase enzyme which results in higher production of estrogen. Adipocytes are capable of producing estrogens, including in the breast tissue in postmenopausal women and in men (48). Furthermore, perturbations in the IGF-1 and insulin axis produced from increased body fatness, lead to a reduction in sex protein-binding globulin, resulting in turn in increased bioavailable estrogens (48). Higher concentrations of estrogen increase cell proliferation through activation of target genes (44; 48). Estrogens can also activate the insulin-signaling pathways (53). This suggests that the interplay of estrogen-related pathways and insulin-signaling pathways may synergistically stimulate cell proliferation. Higher concentrations of leptin, insulin, and inflammatory markers have been shown to stimulate estrogen production and further perpetuate its effects (94). This may further explain the increased proliferation among obese persons and those with perturbations in the insulin-axis. Additionally, estrogens may directly or indirectly cause DNA damage, mutations and genetic instability, contributing to disease progression (88).

Other novel mechanisms—Several other mechanisms underpinning the obesity and cancer link are being speculated. One mechanism is oxidative stress, shown to play a dual role in cell growth and survival. The duality in the role of the pro-oxidants is circumstantial and depends on the pro- and antioxidant ratio of the cell as well as the cell type (38). Additionally, the dysregulation of hormones including glucocorticoid, ghrelin, obestatin, visfatin, and plasminogen activator inhibitor-1 are implicated in tumor development and progression but remain to be elucidated (52; 77; 81).

METHODS

We conducted a systematic literature review to assess the current epidemiologic evidence on the relationship between body adiposity and the prognosis of the three most common obesity-related non-skin cancers: prostate, colorectal, and breast. Although there is substantial evidence of the influence of obesity on the quality of life of cancer survivors, the discussion of these issues is beyond the scope of this review. Understanding the impact of obesity is important because managing body weight could be an important tool for

secondary cancer control. The findings may also provide information critical for guiding clinical practice and strategies for secondary cancer management.

We searched PubMed for papers in the English language that had been published up to July 31, 2011 for articles relevant to breast, prostate, and colorectal cancer. The search process is outlined in Figure 2.

For example, search terms used for breast cancer are shown below:

(Obesity[tiab] OR weight[tiab] OR body mass index[tiab] OR body fat distribution[tiab] OR anthropometric[tiab] OR waist circumference[tiab] OR waist hip ratio*[tiab]) AND (survival[tiab] OR prognosis[tiab] OR progression[tiab] OR recurrence[tiab]) AND (**breast cancer**[tiab]).

We then repeated the above search terms for prostate and colorectal cancer by replacing “breast cancer” with “colorectal cancer”, “colon cancer”, “rectal cancer”, and “prostate cancer” respectively in subsequent searches.

Additionally, we manually searched bibliographies to supplement the online search process.

Inclusion criteria

For the purpose of this review, we only included papers that (*a*) reported estimates for disease-specific mortality or recurrence, (*b*) had a total sample size of at least 200 subjects, (*c*) presented hazard ratios or rate ratios, (*d*) conducted follow-up in cancer cases, and (*e*) presented multivariable analysis.

After excluding the manuscripts that did not meet our inclusion criteria (see Figure 2), a total of 33 articles for breast cancer, six for prostate cancer, and eight for colorectal cancer remained and were included in this review. In presenting the results, we separated findings based on the timing of body mass index (BMI) and/or body weight measurements before and after the cancer diagnosis.

BREAST CANCER MORTALITY AND DISEASE FREE SURVIVAL

Breast cancer is the second leading cause of cancer death (after lung cancer) in women in the United States, accounting for 15% of all cancer deaths in women with the majority of deaths occurring in women 50 years of age or older (23; 101). Survival rates from the disease have improved over the years especially if it is diagnosed at an early stage, a result partly attributed to effective screening and improved treatments. Specifically, the five-year survival rates range from 93% and 88% in stage 0 (cancer is non-invasive) and stage 1 (cancer has not spread to lymph nodes), respectively, to a dismal 15% at stage 4 (cancer has spread beyond the breast and nearby lymph nodes to other organs) (3). Although breast cancer risk is higher among Caucasian women than other ethnic groups, mortality from the disease is highest in African American women (2; 23). African American women appear to have the lowest five-year breast cancer-specific survival rate among all races, which could partly reflect differences in stage of diagnosis, tumor biology, and access to care (23).

Nutritional and anthropometric risk factors for breast cancer include alcohol intake, body fatness and weight gain (for postmenopausal women), and adult attained height, while potential protective factors include lactation, body fatness (for premenopausal women), and physical activity (108; 109). Past reviews on lifestyle factors influencing disease survival have concluded that obesity (13; 66; 86) and a sedentary lifestyle (66) could worsen breast cancer prognosis.

Dosing tolerance of obese women could be underestimated if it is based on ideal body weight, thus potentially leading to underdosing (60). Furthermore, obese women are generally less likely to undergo breast cancer screening (56) and may seek medical attention late, when they already have advanced tumors and other comorbidities that could impact prognosis. However, epidemiological evidence has suggested that a higher (BMI) could also have an independent detrimental effect on survival.

The purpose of this review is to update the evidence on obesity and breast cancer survival, and to summarize the effect of BMI from both before and after a breast cancer diagnosis. We found 33 articles (summarized in Table 1) that investigated obesity and breast cancer recurrence or survival that met our eligibility criteria.

Pre-diagnosis BMI and breast cancer mortality and disease-free survival

Among the 11 studies that reported estimates on breast cancer recurrence (or disease free survival) or breast cancer-- specific mortality based on BMI assessed prior to diagnosis, with the exception of three studies (29; 61; 62) that utilized percentile or unconventional categories for body size, the remaining studies classified obesity based on the World Health Organization classification whereby a BMI ≥ 30 was categorized as obese. Eight of the 10 studies that presented findings on disease mortality (10; 14; 16; 18; 61; 62; 75; 95) consistently suggested an increase in breast cancer-specific mortality for women who were obese as compared to women with normal BMI at least one year prior to diagnosis. Although only three (16; 18; 62) of the eight studies reached statistical significance, the estimates ranged from 20% higher to almost twice the rate for disease mortality in obese women as compared to normal weight women. In contrast, there was no clear evidence of an association in one study (51) whereas a non-significant inverse association was observed in one study (29) that used lower thresholds to categorize body size and only included women 40 years of age or younger at diagnosis with low median BMI. Three studies reported separate estimates for disease recurrence: two of them showed a positive association between obesity and recurrence rates (10; 57), whereas the other one reported no association (51).

Among studies that specifically evaluated the effect of BMI prior to diagnosis by menopausal status, higher mortality and recurrence rates for obese women were noted among both pre- and postmenopausal women diagnosed with breast cancer. However, estimates for disease mortality appeared to be stronger among premenopausal obese women (16; 51), and one study observed stronger recurrence rates among obese postmenopausal women (57). A qualitative difference in effect was only observed in one study (51) where a statistically significant increased mortality rate was observed among obese premenopausal women, and no clear association was observed for postmenopausal women. In contrast, a study that included only premenopausal women (29) reported an inverse association, but lower thresholds for risk assessment and the limited range for BMI in this study group could have potentially limited the ability to detect an association. Overall, it appears that obesity prior to diagnosis has an unfavorable effect on breast cancer prognosis. However, the relationship by menopausal status is uncertain at this time.

Post-diagnosis BMI and breast cancer mortality and disease free survival

We found 22 studies reporting results for the impact of obesity around or after diagnosis on breast cancer mortality and recurrence. The increased rate of mortality or recurrence among obese patients was consistently shown in 14 (6; 10; 14; 22; 26; 31; 42; 71; 74; 75; 87; 98; 103; 107) studies based on BMI measure obtained after diagnosis, although not all estimates reached statistical significance. Eight studies included cases from randomized controlled trials (RCTs) (7; 21; 22; 24; 26; 31; 76; 98). Most of these studies showed modest effects for

disease mortality, although one of them (98) showed stronger effects with BMI > 35. Among studies that reported separate recurrence estimates, the evidence predominantly showed increased rate for recurrence (6; 7; 21; 42; 45; 97; 98). However, a few studies also presented rate ratios below one (64; 72; 76) and null findings (10; 26; 64). Two of the studies that reported an inverse albeit non-significant association included an older study in Austria classifying obesity as a percentage of optimal weight using the Broca formula [(height in centimeters minus 100) minus 10%] (76) and a study conducted in Korea (72), which combined overweight and obese categories.

Studies that presented findings on the effect of BMI (42; 71; 98; 107) or weight of the patient after diagnosis (71) among pre- and/or postmenopausal women consistently showed an increased rate of breast cancer mortality among both premenopausal and postmenopausal obese women. Modest albeit significant estimates for obese premenopausal women were also observed in another study based on RCT data (7). It is intriguing that, among premenopausal women, obesity appears to have an unfavorable impact on breast cancer survival, whereas the inverse is true for breast cancer risk in this group. One prospective cohort that included women only aged 65 years and older showed worse mortality rates in 65-year-olds and a decreasing mortality trend as women got older (87). However, limited sample sizes in the older age strata resulted in low precision of risk estimates.

The predominant reference group used by studies in this review was BMI less than 25 combining the normal weight and underweight categories possibly due to limited cell sizes. However, including both normal and underweight patients in one category could limit the assessment of mortality rates separately in underweight patients. For example, studies that followed the conventional World Health Organization classification and treated only women with BMI between 18.5 and 24.9 as normal weight or the referent, such as the Korean study, observed worse prognosis in underweight patients (HR=1.49; 95% CI: 1.15–1.93) as compared to normal weight women (72). Similarly, a marginally significant association indicating greater mortality among underweight patients as compared to normal weight patients was also observed in another RCT-based study (HR=1.59; 95% CI: 0.97–2.59) (22). In contrast, cohort studies conducted in China and the US did not present convincing evidence, showing increased breast cancer deaths among underweight patients for both BMI before and after diagnosis (14; 75). Estimates remained unchanged even when the Asian classification of BMI was used (103). Limited variation in BMI with most people in the normal weight category (75) was cited as a limitation to detect significant differences.

Although most studies combined all obese women with BMI greater than or equal to 30 into one group, one study that further separated obese from very obese observed the greatest mortality among very obese patients (98). In contrast, two other studies (24; 71) reported similar mortality estimates among obese and very obese women. Exceptions to conventional BMI classification were noted in at least eight studies, where maximum threshold for normal weight was decreased (98), mean values of BMI were utilized in each category (87), quartiles were used (103), or obesity was categorized based on a percentage of ideal weight calculated using height and weight tables or the Broca formula (6; 76; 97). BMI was only reported as a continuous measure in two studies (42; 64), whereas the referent was all non-obese patients (<30) in three studies (45; 57; 71). When authors used actual weight (in pounds) at diagnosis of patients to assess outcomes, an increased rate of breast cancer mortality (HR=1.60; 95% CI: 0.99–2.56) was observed only when the upper threshold for weight was more than 175 pounds as compared to less than 133 pounds among women with early-stage breast cancer (30).

Overall, it appears that being obese immediately after or even few months post diagnosis is an indicator of poor disease prognosis.

Other findings

Waist-to-Hip Ratio (WHR)—We found four studies (8; 14; 18; 103) that examined the impact of WHR on breast cancer mortality. One study found the strongest association with disease mortality among those who were obese and had a high WHR (>0.85) compared to women with normal BMI and $\text{WHR} < 0.85$ ($\text{HR} = 1.57$; 95% CI: 1.08–2.27) (18), whereas a significantly worse mortality rate was only observed among postmenopausal women with high WHR in another study ($\text{RR} = 3.3$; 95% CI: 1.1–10.4) (8). The limited number of outcomes available for the stratified analyses contributed to the lower precision in the second study. No clear evidence of relapse or disease-specific mortality with increasing WHR was observed in the two Asian studies (14; 103).

Estrogen Receptor/Progesterone Receptor Status—No significant estimates were observed for obesity when stratified by estrogen receptor/progesterone receptor (ER/PR) status in two studies (7; 18). One study reported increased deaths for obese women (BMI measured prior to diagnosis) with ER/PR positive tumors and the reverse was true for women with ER/PR-negative tumors (61); i.e. obese patients with ER/PR-negative tumors appeared to have a lower risk of mortality as compared to leaner patients, although analysis in the ER/PR-negative group was based on limited numbers. This finding was also replicated in a study which observed more breast cancer deaths in slim patients with lymph node--positive and ER-negative tumors as compared to obese patients (62). In contrast, one of the two studies conducted in China showed significantly greater relapse and mortality rates among obese women with ER/PR-negative tumors (14). Women who weighed more than 151 pounds and who had ER-negative tumors experienced greater hazard rates ($\text{HR} = 3.47$; 95% CI: 2.11–5.71) than rates observed in heavy women with ER positive tumors (30). One study stratified by hormone replacement therapy use and found the association between obesity and breast cancer mortality to be limited to postmenopausal women who had ever used estrogen-progestin therapy ($\text{HR} = 2.3$; 95% CI: 1.1–5.2) (95).

Weight Change—The effect of weight change on breast cancer mortality or recurrence was assessed in seven studies. Women who gained 5 kg or more from pre-diagnosis to 6 months post-diagnosis had 31% worse survival (95% CI: 0.97–1.75) as compared to losing or gaining 1 kg during the same period (14). This estimate became stronger and significant when this weight change was extended to 18 months post-diagnosis ($\text{HR} = 1.90$; 95% CI: 1.23–2.93) after adjusting for potential covariates. Similarly, a 5 kg gain in weight since diagnosis also increased breast cancer mortality by 13% (95% CI: 1.03–1.25) in another study, and there was no clear association with a decrease of 5 kg (75). This finding was replicated in another study that assessed weight gain by an increase in BMI of 5 kg/m^2 or more as compared with less than 1.5 kg/m^2 from age 30 to diagnosis ($\text{HR} = 1.38$; 95% CI: 1.05–1.83) (18). Weight loss of more than 1 kg also appeared to increase mortality in this study. Of interest was that an increase in BMI by 2 kg/m^2 as compared with no change indicated significant increased hazard of breast cancer-specific death among normal-weight and underweight patients ($\text{RR} = 1.90$; 95% CI: 1.32–2.72) but non-significant inverse effect among obese or overweight patients ($\text{RR} = 0.75$; 95% CI: 0.51–1.11) (51). In contrast, the effect of weight change was not different among normal weight and overweight/obese women in an Asian study (14).

Weight gain from at least 20 years to one year prior to diagnosis seemed to increase breast cancer mortality among both pre- and postmenopausal women (16). However, significant estimates were only observed among postmenopausal women who experienced a weight gain of more than 12.7 kg from 50 years to one year prior to diagnosis when compared to women experiencing a weight change of 3 kg ($\text{HR} = 3.00$; 95% CI: 1.37–6.56). Among women who had normal weight before diagnosis, a BMI change of even 0.5 kg/m^2 appeared

to elevate risk of breast cancer mortality, which further increased with increasing weight gain (51); however these analyses were based on smaller numbers. Increase in weight since age 18, which was evaluated in two studies (29; 107) was not associated with breast cancer-specific mortality.

The only study that specifically assessed the effect of weight change prior to diagnosis on disease recurrence did not show any association when a weight change of more than 10% was compared with a change of 5% (9). Women who were obese prior to diagnosis (HR: 2.5; 95% CI: 1.2–5.1) and women diagnosed with ER/PR negative tumors (HR: 2.0; 95% CI: 1.0–4.4) experienced significant increased recurrence rates as compared to women whose weight had remained stable (10). However, the authors recommended caution in interpreting findings, owing to inherent limitations such as inflated type 1 error. In the same study, gaining weight immediately after diagnosis and up to 4 years was not indicative of a poor prognosis. Change in weight gain or weight loss from pre-diagnosis to study entry did not have any association with disease relapse (9).

In summary, similar to findings about BMI, weight gain after diagnosis appears to be associated with greater disease mortality. However, there is currently limited evidence indicating that weight loss after diagnosis may improve prognosis.

Obesity and breast cancer survival: summary and methodological issues

The current evidence seems to indicate that obesity tends to worsen breast cancer prognosis. The findings were similar irrespective of when obesity was assessed - before, around, or after diagnosis. Furthermore, weight gain after diagnosis also appeared to increase mortality. These findings are consistent with results from other reviews and meta-analyses that have examined the literature on obesity and breast cancer survival using different eligibility criteria (13; 86). However, the limited evidence on improved prognosis with weight loss after diagnosis and the lack of studies separating intentional weight loss from weight loss caused by the disease make it difficult to issue recommendations regarding weight loss for breast cancer survivors. Nevertheless, given the benefits on quality of life and prevention of other chronic diseases, promoting a healthy body weight among cancer survivors seems reasonable.

Certain notable points while interpreting the findings from different studies need to be mentioned. Only six out of the 33 studies included in this review adjusted for lifestyle factors such as physical activity and/or smoking in multivariable models. A recent review on lifestyle factors and cancer survivorship reported beneficial effects of physical activity for cancer survivors (20). Physical activity could favor cancer survival by influencing a reduction in body fat and causing amenable changes in metabolic hormones, growth factors, and adipokines (79). Similarly, smoking is universally known to be related to poor outcomes in general; however specific mechanisms of smoking in influencing breast cancer recurrence are unknown.

In general, it appeared that studies conducted among women participating in clinical trials showed mostly modest effects of obesity on prognosis. This could be partly attributed to the relative homogeneity of the study population with respect to BMI and other important risk factors such as tumor receptor status and stage of disease due to strict inclusion and exclusion criteria, which could potentially result in a group that is healthier to begin with. Furthermore, it is also well known that cancer clinical trial participants are not representative of cancer patients in the general population (17; 49; 80). The time of enrollment or study entry could also influence results. For example, participants in the Life After Cancer Epidemiology study and the Women's Healthy Eating and Living study were not enrolled until after they had completed chemotherapy and/or radiation treatment. As a

result, women who may have experienced recurrence or death in the immediate post diagnosis period were excluded.

It is also important to consider the definition of disease free survival, which varied from including only recurrence events to also including appearance of contralateral tumors and death from any cause if it occurred prior to reporting recurrence. However, most studies presented separate estimates for the different components of disease free survival if it included events other than recurrences. On a similar note, few studies also combined recurrence and disease-specific deaths into one measure, which limited assessing effects of obesity separately on recurrence and mortality.

Several studies in this review obtained height and weight measurements on their participants through objective measures (abstraction from medical records, measurements obtained by trained personnel, etc.), whereas 12 studies utilized self-reported measures. Understandably, self-reported measurements were more often used in studies that assessed the impact of BMI before diagnosis as the subjects may not have come under medical scrutiny before being diagnosed. However, some of these studies demonstrated high correlation between self-reported and measured weight (9; 51; 75). In general, even when there is high correlation between self-reported height and weight and measured height and weight, individuals may tend to overestimate their height and underestimate weight in a systematic way. In such a case, the resulting error would probably lead to an underestimation of the relative risks and hazard ratios in the association between BMI and mortality or recurrence.

To our knowledge, only two studies evaluated the impact of weight gain since age 18 on disease prognosis. Not having information on weight or obesity during early adult years could limit understanding the effects of these risk factors on mortality and recurrence as the impact of these risk factors are generally cumulative in nature. Furthermore, restricting eligibility to studies with a total sample size of at least 200 patients allowed enough outcomes to be observed and estimates to be reported with increased precision. However, sample sizes continued to be limited for stratified analysis in several studies thus restricting statistical power for discerning differences in sub-analyses.

Finally, although racial disparities in breast cancer mortality or survival have been noted, none of the 33 studies included in this review presented race-specific mortality or recurrence estimates, and most of these studies predominantly involved Caucasian women. Given the greater obesity rates among African-American women as compared with white women, evidence assessing racial disparities in the effect of obesity on mortality and disease free survival is limited. Thus, although a recent report on cancer survivorship concluded that there is an overrepresentation of breast cancer survival research efforts when juxtaposed with the proportion of breast cancer survivors (39), there still exists a gap in research addressing racial differences in the association between obesity and breast cancer recurrence and mortality.

In conclusion, current evidence shows that obesity is associated with greater breast cancer-specific-mortality and poor disease-free survival in women diagnosed with the disease.

COLORECTAL CANCER MORTALITY AND DISEASE-FREE SURVIVAL

Based on projections for 2011, colorectal cancer is the third most commonly diagnosed cancer site in the US in men after prostate and lung cancer (101). Colorectal cancer is also the third most common cancer site in women after breast and lung cancer; it accounts for 9% (71,850) and 9% (69,360) of all cancers diagnosed in men and women, respectively (101). Colorectal cancer is also the third leading cause of cancer deaths in the U.S., with an estimated death toll of ~50,000 in 2011. Worldwide statistics are similar to those of the U.S.,

with colorectal cancer being the third most commonly diagnosed cancer among males and second among females (46). Some established relationships with lifestyle factors for colon cancer include an inverse association with physical activity and increased risk with consumption of red and processed meats and alcoholic beverages (108; 110). Furthermore, the WCRF/AICR expert panel concluded that the evidence linking body fatness and colorectal cancer risk was “convincing” (108; 110). Contrary to the consistent direct nature of these relationships in observational studies, evidence for the associations between body adiposity and colorectal cancer survival is sparse, with only eight articles addressing this issue. These are discussed below and summarized in Table 2.

Pre-diagnosis BMI and colorectal cancer mortality

We found three prospective cohort studies reporting on pre-diagnosis BMI in relation to colorectal cancer progression and survival (27; 41; 85). In a prospective Australian study of over 41,500 participants aged between 27 and 75 years, 526 colorectal cancer cases were identified and followed up for an average of 5.5 years during which 181 deaths occurred from colorectal cancer (41). Cancer deaths were ascertained through medical records as well as from the National Death Index. Measures of body adiposity were obtained by trained personnel at baseline prior to cancer diagnosis. This study estimated a 33% increased risk for colorectal cancer mortality for every 10 percent increment of body fat (HR:1.33; 95% CI: 1.04–1.71). Furthermore, there was a 20 % increased risk of colorectal cancer mortality for every 10 cm increase in waist circumference (HR:1.20; 95% CI:1.05–1.37), as well as a 15% increase in disease mortality per 10 kg of body weight (HR:1.15; 95% CI: 1.02–1.29), after adjusting for age, gender, and disease stage. The associations for BMI were in the same direction, although not statistically significant. This study noted no evidence of these associations varying by stage, and associations were not separately presented by sex.

The second prospective study evaluating self-reported pre-cancer anthropometric measures in relation to colon cancer mortality was conducted among women aged 55–69 years (85). Similarly, this study also noted direct associations between higher BMI (BMI > 30) (HR: 1.32, 95% CI: 0.95–1.82), WHR (HR:1.37, 95% CI:1.02–1.85) and waist circumference (HR:1.34; 95% CI: 1.01–1.180) in relation to colon cancer death as compared to women who were lean, after adjusting for age, stage, education and smoking. Conclusions remained unchanged with further adjustment for history of diabetes and heart disease. Stratified analyses by stage revealed stronger association with all anthropometric measurements for distant stage at diagnosis. Consistent with these findings, another study following participants in a case-control study reported elevated colon cancer mortality for obese postmenopausal women (27). In this study, which included 633 colorectal cancer cases identified from the Wisconsin Cancer Reporting System, obese postmenopausal women with a BMI>30.0 kg/m² were approximately at a 2-fold increased risk of colorectal cancer death following the diagnosis of colon cancer (HR: 2.1; 95% CI: 1.1–3.8) after adjusting for age, disease stage, hormone use and smoking. These associations were re-evaluated by use of hormone therapy. The non-significant associations were in a similar direction regardless of hormone use, suggesting a possible independent role of body adiposity. Taken together, the three studies suggest that being obese before a colon cancer diagnosis may increase colorectal cancer mortality. The evidence for rectal cancer is insufficient at this point. More studies are also needed to evaluate the association by gender.

Post- diagnosis BMI and colorectal cancer mortality and disease-free survival

Five studies evaluated colorectal cancer progression or mortality in relation to post-diagnostic BMI (25; 68–70; 102). Dignam et al. (25) evaluated BMI and colon cancer outcomes in participants enrolled in a clinical trial, in which patients with resected colons were randomized to three different chemotherapy regimens. This study noted that patients

with a BMI >35 had a greater risk of colon cancer recurrence (HR: 1.38; 95% CI: 1.10–1.73) and disease-specific mortality (HR: 1.36; 95% CI: 1.06–1.73) after adjusting for type of treatment, age, race, gender, and selected cancer characteristics, compared with normal weight patients. Also, in a study population consisting of a cohort of participants enrolled in seven North Central Cancer Treatment Group chemotherapy trials (n=4,381), those with a BMI >35 kg/m² had poorer disease free survival (HR: 1.23; 95% CI: 1.01–1.49) in comparison to normal-weight patients, and these results remained significant after additional adjustment for age, race, treatment and gender in a multivariable analyses (p=0.03). Local recurrence of disease was similar in obese and normal weight patients. This study was unable to identify disease-specific cause of death; however, disease-free survival was a surrogate for colon cancer mortality in these analyses (102).

Three studies were conducted by Meyerhardt and colleagues using a cohort of patients enrolled in clinical trials. In contrast to the studies discussed above, Meyerhardt et al. did not observe robust evidence of BMI being a strong predictor of colorectal cancer mortality. The first study followed patients enrolled in the Intergroup 0089 trial, a randomized chemotherapy adjuvant trial (n=3759) (68), and noted borderline significant associations of disease recurrence among women with stage II and stage III colon cancer having a BMI >30 kg/m² (HR: 1.24; 95% CI 0.98–1.59) with no association among men (HR: 0.98; 95% CI: 0.79–1.23). Another study conducted within the Intergroup Trial 0114 (70), a four arm randomized trial of rectal cancer patients that compared chemotherapy regimens, with an average follow-up of 11.8 years, noted no significant association between survival or disease recurrence among obese or overweight females. However, although not statistically significant, the HR for 5-year disease free survival and 5-year local recurrence were above one among obese (BMI >30 kg/m²) versus lean men (HR: 1.23; 95% CI: 0.93–1.61 and HR: 1.61; 95% CI: 1.00–2.59, respectively) after adjusting for covariates in this study population. Similarly, in another prospective study in the Cancer and Leukemia Group B 89803 trial (n=1053), BMI was not associated with colon cancer mortality (69). This study evaluated weight change in relation to disease-free survival and recurrence-free survival (defined as tumor recurrence or occurrence of a new primary colon tumor) and found no associations between >5 kg weight gain and the endpoints of interest in multivariable analyses (69).

Obesity and colorectal cancer mortality and disease-free survival: summary and methodological issues

A total of eight studies that investigated BMI in relation to colorectal cancer mortality were included in this review (25; 27; 41; 68–70; 85; 102). The majority of studies utilized BMI measures post-diagnosis of cancer with three studies evaluating BMI prior to cancer diagnosis (27; 41; 85). The evidence from the three evaluating pre-diagnosis BMI was consistent and suggested a 15% to a 2-fold increased risk for colorectal cancer mortality among obese persons (27; 41; 85). The evidence for rectal cancer is insufficient. Results from the studies evaluating BMI after cancer diagnosis were mixed with three studies observing a significant increased risk (25; 27; 102) and three studies observing non-significant increased risk or no association (68–70). It must be noted that the three studies observing non-significant associations were conducted by the same research group which utilized data from clinical trials. Only a minor proportion of cancer patients elect to be enrolled in clinical trials, and obese individuals or those with co-morbidities are less likely to volunteer to participate. Importantly, clinical trials did not have comprehensive data on other lifestyle and behavioral factors that are important cancer risk factors including diet, physical activity, and smoking. These factors are related to inflammation, body weight and insulin resistance and may influence the risk of cancers through several mechanisms. Furthermore, the choice of cancer treatment in obese patients may differ due to poorer

tolerance to treatment. Finally, obese persons are often under-dosed in chemotherapy trials, which may affect the results in these types of studies (55; 84; 93).

Comparing the results of studies with varying study designs is challenging. However, taken together, these studies tend to suggest that measures of body adiposity may be associated with colorectal cancer recurrence and mortality with estimates ranging from 1.2–2.1, albeit not always significant. The relationships of other measures of adiposity particularly abdominal adiposity, which may be a better predictor of colon cancer outcomes (65; 82; 96), were not evaluated in most of these studies. Furthermore, the impact of weight changes on survival has not been addressed in existing studies and therefore warrants investigation. Evidence suggests that timing and duration of exposure to body fatness as well as related metabolic disturbances may be critical in predicting disease outcomes (106). Clearly, additional research in the area of obesity and colorectal cancer survival is needed. In fact, a recent publication revealed that although the colorectal cancer survivors are estimated to be approximately 9% of all cancer survivors, current research focused on colorectal cancer is less than 3%, underscoring the need for additional research (39).

PROSTATE CANCER MORTALITY

Prostate cancer is the leading cancer among men. It accounts for approximately 29% of all cancers with over 240,000 men diagnosed each year (101). It is the second leading cause of cancer death accounting for 11% of all cancer deaths in 2011. Worldwide, prostate cancer is the second most commonly diagnosed cancer after lung cancer and the sixth leading cause of cancer death (46). The few risk factors of prostate cancer that have been identified include age, ethnicity, and heredity (47). Although the modifiable lifestyle and dietary risk factors of prostate cancer are not clear, obesity has been hypothesized to be an important factor having an impact on the progression to advanced prostate cancer and prostate cancer mortality (37; 59; 92). Only six studies (19; 28; 37; 58; 100; 104) were identified meeting our criteria. These are discussed below and summarized in Table 3.

Pre-diagnosis BMI and prostate cancer mortality

Two studies evaluated the impact of pre-diagnostic BMI on prostate cancer mortality (37; 58). In the first study, which was conducted by Ma et al. among 2,546 men diagnosed with prostate cancer who participated in the Health Professionals Follow-Up Study, obese men had a significantly higher risk of dying from prostate cancer compared to those with a normal BMI (HR:1.95; 95% CI: 1.17–3.23) after adjusting for age, smoking, time from BMI measurement, clinical stage, and Gleason grade (a measure of prostate cancer severity) (58). However, a major limitation of this study was the inability of the authors to control for prostate-specific antigen (PSA) screening and cancer treatment. The latter is important because prostate cancer death may have been in part influenced by choice of treatment rather than obesity. In the other study (37), 752 middle aged men with prostate cancer were followed up after enrollment into a case-control study. BMI was self-reported for 1 year prior to diagnosis at the time of interview. In this study a BMI of 30 kg/m² or higher was associated with a significant increased risk for prostate cancer mortality (HR:2.64; 95% CI: 1.18–5.92) after adjusting for age, race, smoking status, Gleason score, stage at diagnosis, diagnostic PSA concentrations, and treatment. Furthermore, obese men with a BMI >30 kg/m² were at increased risk of metastasis (HR:3.61; 95% CI: 1.73–7.51). Associations were similar regardless of treatment and when stratified by Gleason score.

Post-diagnosis BMI and prostate cancer mortality

Among the included studies in this review, four evaluated BMI measured after cancer diagnosis in relation to prostate cancer mortality (19; 28; 100; 104). In one study, men with

localized prostate cancer (n=788) were followed-up for prostate cancer-specific mortality (28). BMI was ascertained at time of radical prostatectomy and radiotherapy. In multivariable analyses BMI was associated with higher risk of dying of prostate cancer for overweight (HR:1.52; 95% CI:1.02, 2.28) and obese men (HR:1.64; 95% CI: 1.01–2.66). Van Roermund et al. (104) also found increased, although not statistically significant, prostate cancer mortality (HR: 1.46; 95% CI: 0.50–4.28) for obese men in a retrospective cohort study conducted in the Netherlands. In contrast, the prospective CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) study, with a mean follow-up period of approximately 4 years found no associations between BMI and prostate cancer-specific mortality (19). Additionally, a prospective cohort study conducted using the Mayo Clinic Prostatectomy Registry (approximate follow-up time of 10 years) noted no influence of obesity on prostate cancer survival (100)

A recent systematic review and meta-analysis of six population-based studies investigating BMI and mortality from prostate cancer among 1,263,483 men who were cancer-free at baseline (6,817 prostate cancer deaths), revealed that a 5 kg/m² BMI was associated with a 15% increased risk of prostate cancer (HR: 1.15; 95% CI: 1.06–1.25) and in studies that followed up patients after the diagnosis of cancer, there was a 20% increase in risk of prostate cancer-specific mortality, which was borderline significant (HR: 1.20; 95% CI: 0.99–1.46; p=0.06) (12). The population attributable rate of overweight and obesity on prostate cancer -specific mortality was 20% with approximately 11% being attributed to overweight and 9% to obesity (12). These remained significant after adjusting for Gleason grade and clinical stage. It must be noted that studies in which BMI was measured both before and after cancer diagnosis were combined in the meta-analyses.

Body mass index and prostate cancer recurrence and biochemical failure after diagnosis

Although there are considerable data on the relationships of body adiposity and biochemical failure (measured by serum PSA re-elevation) it is beyond the scope of this review to discuss the individual studies investigating this issue. However, a recent meta-analysis of 17 studies, including 12 studies in which the primary treatment was radical prostatectomy and 5 studies in which the primary treatment was radio- or brachytherapy (with or without androgen deprivation therapy) revealed that regardless of treatment type, there was a 21% to 25% increase in recurrence or biochemical failure in patients with a 5 kg/m² BMI(12).

Obesity and prostate cancer mortality: summary and methodological issues

Although the evidence is not entirely consistent, studies overall have suggested that higher BMI is associated with increased risk of dying from prostate cancer. However, some limitations of the current body of evidence should be noted when interpreting results. Obese men are less likely to get screened for prostate cancer (111) and, therefore, may present with more aggressive prostate cancer when the cancer is detected. Thus, obesity could increase prostate cancer mortality at least in part, due to a more likely diagnosis of aggressive disease at the time of diagnosis. However, some of the studies adjusted for stage at diagnosis and still found an association (28; 69). Next, several studies included in this review did not adjust for competing causes of death. In the post-PSA era, prostate cancer is being detected at earlier stages, and men with localized tumors are more likely to die of other chronic diseases rather than prostate cancer-specific death; these other causes of death need to be accounted for in the analytic strategy. Finally, studies that were based on existing clinical trials had a shorter follow-up time as compared with observational studies and tended to have more detailed information on treatment variables than on behavioral risk factors. For instance, physical activity, diet and smoking may influence the risk of prostate cancer mortality by direct effects or through body weight. However, these factors were not always considered in the analyses and interpretation of the studies.

Another important issue to consider is the metabolic repercussions of androgen deprivation therapy that is commonly given to patients who have been detected with early stage prostate cancer, particularly in the recent PSA era. Long-term depletion of androgen post-diagnosis may induce obesity and related metabolic alterations which could create an environment conducive to cancer progression.

In summary, the current body of evidence suggests that obesity is associated with clinically significant outcomes of prostate cancer. However, few studies address these relationships and, to our knowledge, no studies have evaluated the impact of intentional weight loss on prostate cancer survival. Therefore, it may be premature to draw any conclusions on the basis of the limited epidemiologic evidence.

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

This review was undertaken to assess the current evidence of the impact of body adiposity on clinically significant cancer outcomes, with a focus on breast, prostate, and colorectal cancer survivors. Taken together, studies have generally suggested that higher body adiposity (measured as BMI in the majority of the studies reviewed) may decrease survival. However, most of the studies were not specifically designed to evaluate these issues, and some failed to control for other lifestyle factors that may affect survival, such as physical activity, alcohol intake, and other relevant factors. Furthermore, because obese patients may be underdosed or have different treatment regimens based on comorbidities, studies should adjust for treatment (modalities and dosage), which has not always been done. As previously mentioned, some of the studies were based on data collected in clinical trials designed to evaluate various chemotherapy regimens. This is of concern, as participants in clinical trials tend not to be representative of all cases, and obese patients and minorities are particularly underrepresented.

Cancer survivorship is an emerging topic of high scientific interest. As obesity continues to represent a significant public health issue as well as being highly prevalent among cancer patients (50; 63), assessing its long-term impact in the growing population of cancer survivors is of paramount importance. Clearly, more research is needed for all cancer sites. Studies need to be designed to evaluate the impact of obesity before and after diagnosis as well as the effects of weight changes, specifically intentional weight loss. Studies in minorities, which have higher prevalence of obesity and reduced survival for most cancers, are particularly needed. More evidence regarding the impact of obesity and weight changes on cancer survival is urgently needed to inform interventions in cancer survivors and improve clinical management of cancer, with the ultimate goal of improving survival and quality of life in cancer survivors.

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References

1. Altekruse, S.; Kosary, C.; Krapcho, M.; Neyman, N.; Aminou, R.; Waldron, W. SEER cancer statistics review, 1975–2008. [Based on November 2010 SEER data submission posted to the SEER website: http://seer.cancer.gov/csr/1975_2007/]
2. American Cancer Society. [Accessed November 7, 2011] Cancer Facts & Figures 2011. 2011. <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-029771.pdf>

3. American Cancer Society. [Accessed September 26, 2011] Survival rates for breast cancer. 2011. <http://www.cancer.org/Cancer/BreastCancer/OverviewGuide/breast-cancer-overview-survival-rates>
4. Barb D, Williams CJ, Neuwirth AK, Mantzoros CS. Adiponectin in relation to malignancies: a review of existing basic research and clinical evidence. *The American Journal of Clinical Nutrition*. 2007; 86:858S–66S.
5. Basen-Engquist K, Scruggs S, Jhingran A, Bodurka DC, Lu K, et al. Physical activity and obesity in endometrial cancer survivors: associations with pain, fatigue, and physical functioning. *American Journal of Obstetrics and Gynecology*. 2009; 200:288.e1–e8. [PubMed: 19110220]
6. Bastarrachea J, Hortobagyi GN, Smith TL, Kau SW, Buzdar AU. Obesity as an adverse prognostic factor for patients receiving adjuvant chemotherapy for breast cancer. *Ann Intern Med*. 1994; 120:18–25. [PubMed: 8250452]
7. Berclaz G, Li S, Price KN, Coates AS, Castiglione-Gertsch M, et al. Body mass index as a prognostic feature in operable breast cancer: the International Breast Cancer Study Group experience. *Ann Oncol*. 2004; 15:875–84. [PubMed: 15151943]
8. Borugian MJ, Sheps SB, Kim-Sing C, Olivotto IA, Van Patten C, et al. Waist-to-hip ratio and breast cancer mortality. *Am J Epidemiol*. 2003; 158:963–8. [PubMed: 14607804]
9. Caan BJ, Emond JA, Natarajan L, Castillo A, Gunderson EP, et al. Post-diagnosis weight gain and breast cancer recurrence in women with early stage breast cancer. *Breast Cancer Res Treat*. 2006; 99:47–57. [PubMed: 16541317]
10. Caan BJ, Kwan ML, Hartzell G, Castillo A, Slaterry ML, et al. Pre-diagnosis body mass index, post-diagnosis weight change, and prognosis among women with early stage breast cancer. *Cancer Causes Control*. 2008; 19:1319–28. [PubMed: 18752034]
11. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults. *New England Journal of Medicine*. 2003; 348:1625–38. [PubMed: 12711737]
12. Cao Y, Ma J. Body Mass Index, Prostate Cancer-Specific Mortality, and Biochemical Recurrence: a Systematic Review and Meta-analysis. *Cancer Prevention Research*. 2011; 4:486–501. [PubMed: 21233290]
13. Carmichael AR. Obesity and prognosis of breast cancer. *Obes Rev*. 2006; 7:333–40. [PubMed: 17038127]
14. Chen X, Lu W, Zheng W, Gu K, Chen Z, et al. Obesity and weight change in relation to breast cancer survival. *Breast Cancer Res Treat*. 2010; 122:823–33. [PubMed: 20058068]
15. Choi KM, Ryu OH, Lee KW, Kim HY, Seo JA, et al. Serum adiponectin, interleukin-10 levels and inflammatory markers in the metabolic syndrome. *Diabetes Res Clin Pract*. 2006
16. Cleveland RJ, Eng SM, Abrahamson PE, Britton JA, Teitelbaum SL, et al. Weight gain prior to diagnosis and survival from breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2007; 16:1803–11. [PubMed: 17855698]
17. Cottin V, Arpin D, Lasset C, Cordier JF, Brune J, et al. Small-cell lung cancer: patients included in clinical trials are not representative of the patient population as a whole. *Ann Oncol*. 1999; 10:809–15. [PubMed: 10470428]
18. Dal Maso L, Zucchetto A, Talamini R, Serraino D, Stocco CF, et al. Effect of obesity and other lifestyle factors on mortality in women with breast cancer. *Int J Cancer*. 2008; 123:2188–94. [PubMed: 18711698]
19. Davies BJ, Smaldone MC, Sadetsky N, Dall'era M, Carroll PR. The Impact of Obesity on Overall and Cancer Specific Survival in Men With Prostate Cancer. *The Journal of Urology*. 2009; 182:112–7. [PubMed: 19447437]
20. 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. [PubMed: 22048034]
21. Dawood S, Broglio K, Gonzalez-Angulo AM, Kau SW, Islam R, et al. Prognostic value of body mass index in locally advanced breast cancer. *Clin Cancer Res*. 2008; 14:1718–25. [PubMed: 18347172]
22. de Azambuja E, McCaskill-Stevens W, Francis P, Quinaux E, Crown JP, et al. The effect of body mass index on overall and disease-free survival in node-positive breast cancer patients treated with

- docetaxel and doxorubicin-containing adjuvant chemotherapy: the experience of the BIG 02-98 trial. *Breast Cancer Res Treat.* 2010; 119:145–53. [PubMed: 19731015]
23. Desantis C, Siegel R, Bandi P, Jemal A. Breast cancer statistics, 2011. *CA Cancer J Clin.* 2011
 24. Dignam J, Wieand K, Johnson K, Raich P, Anderson S, et al. Effects of obesity and race on prognosis in lymph node-negative, estrogen receptor-negative breast cancer. *Breast Cancer Research and Treatment.* 2006; 97:245–54. [PubMed: 16331345]
 25. Dignam JJ, Polite BN, Yothers G, Raich P, Colangelo L, et al. Body Mass Index and Outcomes in Patients Who Receive Adjuvant Chemotherapy for Colon Cancer. *Journal of the National Cancer Institute.* 2006; 98:1647–54. [PubMed: 17105987]
 26. Dignam JJ, Wieand K, Johnson KA, Fisher B, Xu L, Mamounas EP. Obesity, tamoxifen use, and outcomes in women with estrogen receptor-positive early-stage breast cancer. *J Natl Cancer Inst.* 2003; 95:1467–76. [PubMed: 14519753]
 27. Doria-Rose V, Newcomb P, Morimoto L, Hampton J, Trentham-Dietz A. Body Mass Index and the Risk of Death Following the Diagnosis of Colorectal Cancer in Postmenopausal Women (United States). *Cancer Causes and Control.* 2006; 17:63–70. [PubMed: 16411054]
 28. Efsthathiou JA, Bae K, Shipley WU, Hanks GE, Pilepich MV, et al. Obesity and mortality in men with locally advanced prostate cancer. *Cancer.* 2007; 110:2691–9. [PubMed: 17999404]
 29. Enger SM, Bernstein L. Exercise activity, body size and premenopausal breast cancer survival. *Br J Cancer.* 2004; 90:2138–41. [PubMed: 15150561]
 30. Enger SM, Greif JM, Polikoff J, Press M. Body weight correlates with mortality in early-stage breast cancer. *Arch Surg.* 2004; 139:954–58. discussion 8–60. [PubMed: 15381612]
 31. Ewertz M, Jensen MB, Gunnarsdottir KA, Hojris I, Jakobsen EH, et al. Effect of obesity on prognosis after early-stage breast cancer. *J Clin Oncol.* 2011; 29:25–31. [PubMed: 21115856]
 32. Fain JN, Madan AK, Hiler ML, Cheema P, Bahouth SW. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. *Endocrinology.* 2004; 145:2273–82. [PubMed: 14726444]
 33. Fantuzzi G. Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol.* 2005; 115:911–9. quiz 20. [PubMed: 15867843]
 34. Fischer S, Hanefeld M, Haffner SM, Fusch C, Schwanebeck U, et al. Insulin-resistant patients with type 2 diabetes mellitus have higher serum leptin levels independently of body fat mass. *Acta Diabetologica.* 2002; 39:105–10. [PubMed: 12357293]
 35. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and Trends in Obesity Among US Adults, 1999–2008. *JAMA: The Journal of the American Medical Association.* 2010; 303:235–41. [PubMed: 20071471]
 36. Frankenberry KA, Somasundar P, McFadden DW, Vona-Davis LC. Leptin induces cell migration and the expression of growth factors in human prostate cancer cells. *Am J Surg.* 2004; 188:560–5. [PubMed: 15546570]
 37. Gong Z, Neuhaus ML, Goodman PJ, Albanes D, Chi C, et al. Obesity, Diabetes, and Risk of Prostate Cancer: Results from the Prostate Cancer Prevention Trial. *Cancer Epidemiology Biomarkers & Prevention.* 2006; 15:1977–83.
 38. Halliwell B. Oxidative stress and cancer: have we moved forward? *Biochem J.* 2007; 401:1–11. [PubMed: 17150040]
 39. Harrop JP, Dean JA, Paskett ED. Cancer Survivorship Research: A Review of the Literature and Summary of Current NCI-Designated Cancer Center Projects. *Cancer Epidemiol Biomarkers Prev.* 2011; 20:2042–7. [PubMed: 21980012]
 40. Hausman GJ, Richardson RL. Adipose tissue angiogenesis. *J Anim Sci.* 2004; 82:925–34. [PubMed: 15032451]
 41. Haydon AMM, MacInnis RJ, English DR, Giles GG. Effect of physical activity and body size on survival after diagnosis with colorectal cancer. *Gut.* 2006; 55:62–7. [PubMed: 15972299]
 42. Hebert JR, Hurley TG, Ma Y. The effect of dietary exposures on recurrence and mortality in early stage breast cancer. *Breast Cancer Res Treat.* 1998; 51:17–28. [PubMed: 9877026]
 43. Hursting SD, Berger NA. Energy balance, host-related factors, and cancer progression. *J Clin Oncol.* 2010; 28:4058–65. [PubMed: 20697088]

44. Hursting SD, Lashinger LM, Wheatley KW, Rogers CJ, Colbert LH, et al. Reducing the weight of cancer: mechanistic targets for breaking the obesity-carcinogenesis link. *Best Pract Res Clin Endocrinol Metab.* 2008; 22:659–69. [PubMed: 18971125]
45. Imkamp AK, Bates T. Impact of a raised body mass index on breast cancer survival in relation to age and disease extent at diagnosis. *Breast J.* 2010; 16:156–61. [PubMed: 19968656]
46. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA: a cancer journal for clinicians.* 2011; 61:69–90. [PubMed: 21296855]
47. Jemal A, Siegel R, Xu J, Ward E. Cancer Statistics, 2010. *CA Cancer J Clin.* 2010; 60:277–300. [PubMed: 20610543]
48. Kaaks R, Lukanova A. Energy balance and cancer: the role of insulin and insulin-like growth factor-I. *Proceedings of the Nutrition Society.* 2001; 60:91–106. [PubMed: 11310428]
49. Kalata P, Martus P, Zettl H, Rodel C, Hohenberger W, et al. Differences between clinical trial participants and patients in a population-based registry: the German Rectal Cancer Study vs. the Rostock Cancer Registry. *Dis Colon Rectum.* 2009; 52:425–37. [PubMed: 19333042]
50. Kim HS, Moreira DM, Smith MR, Presti JC, Aronson WJ, et al. A natural history of weight change in men with prostate cancer on androgen-deprivation therapy (ADT): results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. *BJU International.* 2011; 107:924–8. [PubMed: 20860651]
51. Kroenke CH, Chen WY, Rosner B, Holmes MD. Weight, weight gain, and survival after breast cancer diagnosis. *J Clin Oncol.* 2005; 23:1370–8. [PubMed: 15684320]
52. Kwaan HC, Wang J, Svoboda K, Declerck PJ. Plasminogen activator inhibitor 1 may promote tumour growth through inhibition of apoptosis. *Br J Cancer.* 2000; 82:1702–8. [PubMed: 10817507]
53. Lee AVJJ, Gooch JL, Hilsenbeck SG, Coronado-Heinson E, Osborne CK, Yee D. Enhancement of insulin-like growth factor signaling in human breast cancer: estrogen regulation of insulin receptor substrate-1 expression in vitro and in vivo. *Mol Endocrinol.* 1999; 5:153–65.
54. Leyva F, Godsland IF, Gbatei M, Proudler AJ, Aldis S, et al. Hyperleptinemia as a component of a metabolic syndrome of cardiovascular risk. *Arterioscler Thromb Vasc Biol.* 1998; 18:928–33. [PubMed: 9633933]
55. Lind MJ, Margison JM, Cerny T, Thatcher N, Wilkinson PM. Prolongation of ifosfamide elimination half-life in obese patients due to altered drug distribution. *Cancer Chemotherapy and Pharmacology.* 1989; 25:139–42. [PubMed: 2557169]
56. Littman AJ, Koepsell TD, Forsberg CW, Boyko EJ, Yancy WS Jr. Preventive care in relation to obesity: an analysis of a large, national survey. *Am J Prev Med.* 2011; 41:465–72. [PubMed: 22011416]
57. Loi S, Milne RL, Friedlander ML, McCredie MR, Giles GG, et al. Obesity and outcomes in premenopausal and postmenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2005; 14:1686–91. [PubMed: 16030102]
58. Ma J, Li H, Giovannucci E, Mucci L, Qiu W, et al. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. *The Lancet Oncology.* 2008; 9:1039–47. [PubMed: 18835745]
59. MacInnis RJ, English DR, Gertig DM, Hopper JL, Giles GG. Body Size and Composition and Prostate Cancer Risk. *Cancer Epidemiology Biomarkers & Prevention.* 2003; 12:1417–21.
60. Madarnas Y, Sawka CA, Franssen E, Bjarnason GA. Are medical oncologists biased in their treatment of the large woman with breast cancer? *Breast Cancer Res Treat.* 2001; 66:123–33. [PubMed: 11437098]
61. Maehle BO, Tretli S. Pre-morbid body-mass-index in breast cancer: reversed effect on survival in hormone receptor negative patients. *Breast Cancer Res Treat.* 1996; 41:123–30. [PubMed: 8944330]
62. Maehle BO, Tretli S, Thorsen T. The associations of obesity, lymph node status and prognosis in breast cancer patients: dependence on estrogen and progesterone receptor status. *APMIS.* 2004; 112:349–57. [PubMed: 15511272]

63. Makari-Judson G, Judson CH, Mertens WC. Longitudinal Patterns of Weight Gain after Breast Cancer Diagnosis: Observations beyond the First Year. *The Breast Journal*. 2007; 13:258–65. [PubMed: 17461900]
64. Marret H, Perrotin F, Bougnoux P, Descamps P, Hubert B, et al. Low body mass index is an independent predictive factor of local recurrence after conservative treatment for breast cancer. *Breast Cancer Res Treat*. 2001; 66:17–23. [PubMed: 11368406]
65. Martínez ME, Giovannucci E, Spiegelman D, Willett WC, Hunter DJ, Colditz GA. Leisure-Time Physical Activity, Body Size, and Colon Cancer in Women. *Journal of the National Cancer Institute*. 1997; 89:948–55. [PubMed: 9214674]
66. McTiernan A, Irwin M, Vongruenigen V. Weight, physical activity, diet, and prognosis in breast and gynecologic cancers. *J Clin Oncol*. 2010; 28:4074–80. [PubMed: 20644095]
67. Meric-Bernstam F, Gonzalez-Angulo AM. Targeting the mTOR signaling network for cancer therapy. *J Clin Oncol*. 2009; 27:2278–87. [PubMed: 19332717]
68. Meyerhardt JA, Catalano PJ, Haller DG, Mayer RJ, Benson AB, et al. Influence of body mass index on outcomes and treatment-related toxicity in patients with colon carcinoma. *Cancer*. 2003; 98:484–95. [PubMed: 12879464]
69. Meyerhardt JA, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, 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. *Journal of Clinical Oncology*. 2008; 26:4109–15. [PubMed: 18757324]
70. Meyerhardt JA, Tepper JE, Niedzwiecki D, Hollis DR, McCollum AD, 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. *Journal of Clinical Oncology*. 2004; 22:648–57. [PubMed: 14966087]
71. Mohle-Boetani JC, Grosser S, Whittemore AS, Malec M, Kampert JB, Paffenbarger RS Jr. Body size, reproductive factors, and breast cancer survival. *Prev Med*. 1988; 17:634–42. [PubMed: 3237661]
72. Moon HG, Han W, Noh DY. Underweight and breast cancer recurrence and death: a report from the Korean Breast Cancer Society. *J Clin Oncol*. 2009; 27:5899–905. [PubMed: 19805676]
73. Mosher CE, Sloane R, Morey MC, Snyder DC, Cohen HJ, et al. Associations between lifestyle factors and quality of life among older long-term breast, prostate, and colorectal cancer survivors. *Cancer*. 2009; 115:4001–9. [PubMed: 19637244]
74. Newman SC, Lees AW, Jenkins HJ. The effect of body mass index and oestrogen receptor level on survival of breast cancer patients. *Int J Epidemiol*. 1997; 26:484–90. [PubMed: 9222771]
75. Nichols HB, Trentham-Dietz A, Egan KM, Titus-Ernstoff L, Holmes MD, et al. Body mass index before and after breast cancer diagnosis: associations with all-cause, breast cancer, and cardiovascular disease mortality. *Cancer Epidemiol Biomarkers Prev*. 2009; 18:1403–9. [PubMed: 19366908]
76. Obermair A, Kurz C, Hanzal E, Bancher-Todesca D, Thoma M, et al. The influence of obesity on the disease-free survival in primary breast cancer. *Anticancer Res*. 1995; 15:2265–9. [PubMed: 8572635]
77. Park J-W, Kim W-H, Shin S-H, Kim JY, Yun MR, et al. Visfatin exerts angiogenic effects on human umbilical vein endothelial cells through the mTOR signaling pathway. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*. 2011; 1813:763–71.
78. Parry C, Kent EE, Mariotto AB, Alfano CM, Rowland JH. Cancer Survivors: A Booming Population. *Cancer Epidemiology Biomarkers & Prevention*. 2011; 20:1996–2005.
79. Pekmezi DW, Demark-Wahnefried W. Updated evidence in support of diet and exercise interventions in cancer survivors. *Acta Oncol*. 2011; 50:167–78. [PubMed: 21091401]
80. Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet*. 2004; 363:263–70. [PubMed: 14751698]
81. Perks CM, Holly JMP. Hormonal Mechanisms Underlying the Relationship Between Obesity and Breast Cancer. *Endocrinology & Metabolism Clinics of North America*. 2011; 40:485–507. [PubMed: 21889716]

82. Pischon T, Lahmann PH, Boeing H, Friedenreich C, Norat T, et al. Body Size and Risk of Colon and Rectal Cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *Journal of the National Cancer Institute*. 2006; 98:920–31. [PubMed: 16818856]
83. Pittas AG, Joseph NA, Greenberg AS. Adipocytokines and insulin resistance. *J Clin Endocrinol Metab*. 2004; 89:447–52. [PubMed: 14764746]
84. Powis G, Reece P, Ahmann DL, Ingle JN. Effect of body weight on the pharmacokinetics of cyclophosphamide in breast cancer patients. *Cancer Chemotherapy and Pharmacology*. 1987; 20:219–22. [PubMed: 3315280]
85. Prizment AE, Flood A, Anderson KE, Folsom AR. Survival of Women with Colon Cancer in Relation to Precancer Anthropometric Characteristics: the Iowa Women's Health Study. *Cancer Epidemiology Biomarkers & Prevention*. 2010; 19:2229–37.
86. 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. [PubMed: 20571870]
87. Reeves KW, Faulkner K, Modugno F, Hillier TA, Bauer DC, et al. Body mass index and mortality among older breast cancer survivors in the Study of Osteoporotic Fractures. *Cancer Epidemiol Biomarkers Prev*. 2007; 16:1468–73. [PubMed: 17627012]
88. Renehan AG, Roberts DL, Dive C. Obesity and cancer: pathophysiological and biological mechanisms. *Arch Physiol Biochem*. 2008; 114:71–83. [PubMed: 18465361]
89. Ries LAGM, D.; Krapcho, M.; Mariotto, A.; Miller, BA.; Feuer, EJ.; Clegg, L.; Horner, MJ.; Howlander, N.; Eisner, MP.; Reichman, M.; Edwards, BK., editors. *SEER Cancer Statistics Review, 1975–2004*. National Cancer Institute; Bethesda, MD: 2007.
90. Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. *Annu Rev Med*. 2010; 61:301–16. [PubMed: 19824817]
91. Robison LL, Demark-Wahnefried W. Cancer Survivorship: Focusing on Future Research Opportunities. *Cancer Epidemiology Biomarkers & Prevention*. 2011; 20:1994–5.
92. Rodriguez C, Freedland SJ, Deka A, Jacobs EJ, McCullough ML, et al. Body Mass Index, Weight Change, and Risk of Prostate Cancer in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiology Biomarkers & Prevention*. 2007; 16:63–9.
93. Rodvold KA, Rushing DA, Tewksbury DA. Doxorubicin clearance in the obese. *Journal of Clinical Oncology*. 1988; 6:1321–7. [PubMed: 3411343]
94. Rose DP, Komninou D, Stephenson GD. Obesity, adipocytokines, and insulin resistance in breast cancer. *Obesity Reviews*. 2004; 5:153–65. [PubMed: 15245384]
95. Rosenberg L, Czene K, Hall P. Obesity and poor breast cancer prognosis: an illusion because of hormone replacement therapy? *Br J Cancer*. 2009; 100:1486–91. [PubMed: 19367278]
96. Russo A, Franceschi S, La Vecchia C, Dal Maso L, Montella M, et al. Body size and colorectal-cancer risk. *International Journal of Cancer*. 1998; 78:161–5.
97. Senie RT, Rosen PP, Rhodes P, Lesser ML, Kinne DW. Obesity at diagnosis of breast carcinoma influences duration of disease-free survival. *Ann Intern Med*. 1992; 116:26–32. [PubMed: 1727092]
98. Sestak I, Distler W, Forbes JF, Dowsett M, Howell A, Cuzick J. Effect of body mass index on recurrences in tamoxifen and anastrozole treated women: an exploratory analysis from the ATAC trial. *J Clin Oncol*. 2010; 28:3411–5. [PubMed: 20547990]
99. Sharma D, Saxena NK, Vertino PM, Anania FA. Leptin promotes the proliferative response and invasiveness in human endometrial cancer cells by activating multiple signal-transduction pathways. *Endocr Relat Cancer*. 2006; 13:629–40. [PubMed: 16728588]
100. Siddiqui SA, Inman BA, Sengupta S, Slezak JM, Bergstralh EJ, et al. Obesity and survival after radical prostatectomy: A 10-year prospective cohort study. *Cancer*. 2006; 107:521–9. [PubMed: 16773619]
101. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin*. 2011; 61:212–36. [PubMed: 21685461]

102. Sinicrope FA, Foster NR, Sargent DJ, O'Connell MJ, Rankin C. Obesity Is an Independent Prognostic Variable in Colon Cancer Survivors. *Clinical Cancer Research*. 2010; 16:1884–93. [PubMed: 20215553]
103. Tao MH, Shu XO, Ruan ZX, Gao YT, Zheng W. Association of overweight with breast cancer survival. *Am J Epidemiol*. 2006; 163:101–7. [PubMed: 16339054]
104. van Roermund JG, Hinnen KA, Battermann JJ, Witjes JA, Bosch JL, et al. Body mass index is not a prognostic marker for prostate-specific antigen failure and survival in Dutch men treated with brachytherapy. *BJU Int*. 2010; 105:42–8. [PubMed: 19519759]
105. Wauters M, Considine RV, Yudkin JS, Peiffer F, De Leeuw I, Van Gaal LF. Leptin levels in type 2 diabetes: associations with measures of insulin resistance and insulin secretion. *Horm Metab Res*. 2003; 35:92–6. [PubMed: 12734788]
106. Wei EK, Wolin KY, Colditz GA. Time Course of Risk Factors in Cancer Etiology and Progression. *Journal of Clinical Oncology*. 2010; 28:4052–7. [PubMed: 20644083]
107. Whitman MK, Hillis SD, Curtis KM, McDonald JA, Wingo PA, Marchbanks PA. Body mass and mortality after breast cancer diagnosis. *Cancer Epidemiol Biomarkers Prev*. 2005; 14:2009–14. [PubMed: 16103453]
108. World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. AICR; Washington DC: 2007.
109. World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Breast Cancer. 2010.
110. World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer. 2011.
111. Wright ME, Chang S-C, Schatzkin A, Albanes D, Kipnis V, et al. Prospective study of adiposity and weight change in relation to prostate cancer incidence and mortality. *Cancer*. 2007; 109:675–84. [PubMed: 17211863]
112. Yabroff KR, Lund J, Kepka D, Mariotto A. Economic Burden of Cancer in the United States: Estimates, Projections, and Future Research. *Cancer Epidemiology Biomarkers & Prevention*. 2011; 20:2006–14.
113. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol*. 1999; 19:972–8. [PubMed: 10195925]

Figure 1.
Potential underlying biological mechanism of obesity and cancer progression

Figure 2.
Search process for articles

Table 1
Studies evaluating body mass index (BMI) and breast cancer mortality and disease-free survival (n=33)

Reference	Location	Design	Sample (n)	Time of exposure	Contrast	RR/HR (95% CI)	Outcome	Covariates
(71)	U.S.	Follow-up of cases in a case-control study	838 257 deaths	<i>Post-diagnosis</i> BMI	34.7 vs 30.4		Disease mortality	Age at diagnosis, stage at diagnosis, period of follow-up
					All women	1.4 (p=0.02)		
					<i>Premenopausal</i>	1.6 (p=0.08)		
					<i>Postmenopausal</i>	1.3 (p=0.08)		
					30.5–34.6 vs 30.4			
					All women	1.5 (p=0.02)		
					<i>Premenopausal</i>	1.6 (p=0.08)		
(97)	U.S.	Prospective cohort	923 380 recurrences	<i>Post-diagnosis</i> BMI	<i>postmenopausal</i>	1.4 (p=0.08)	Disease free survival	Tumor size, number of positive axillary lymph nodes, age at diagnosis, adjuvant chemotherapy
					>140 vs 140	1.1 (p=0.32)		
					All women	1.7 (p=0.04)		
					<i>Premenopausal</i>			
					<i>postmenopausal</i>	1.0 (p=1.0)		
					25% over optimal weight for height vs <25%	1.29 (1.0–1.67)		
(6)	U.S.	Retrospective cohort	735	<i>Post-diagnosis</i> BMI	20% of ideal weight vs ideal weight	1.33 (1.05–1.68)	Disease free survival	Menopausal status, stage, number of involved nodes
			298 deaths					
			362 recurrences			1.36 (1.06–1.76)	Disease specific survival	
(76)	Austria	Follow-up of cases from an RCT	473 133 recurrences	<i>Post-diagnosis</i> (used Broca formula)	Obese vs normal weight	0.83 (0.55–1.24)	Disease free survival	Lymph node involvement, grading, tumor size, ER, PR, menopausal status

Reference	Location	Design	Sample (n)	Time of exposure	Contrast	RR/HR (95% CI)	Outcome	Covariates
(61)	Norway	Prospective cohort	1238 339 deaths	<i>Pre-diagnosis</i> BMI (quintiles)	Fifth vs first	1.37 (0.99–1.90)	Disease specific survival	Age, lymph node status, tumor size, mean nuclear area
(74)	Canada	Prospective cohort	1169	<i>Post-diagnosis</i> BMI	>28.9 vs <22.8	2.47 (1.17–5.22)	Disease-specific survival	Tumor size, number of positive nodes, estrogen receptor, age
(42)	U.S.	Prospective cohort	472 190 recurrences 73 deaths	<i>Post-diagnosis</i> BMI	Continuous All women <i>Premenopausal</i> All women <i>Premenopausal</i>	1.04 (1.00–1.09) 1.09 (1.02–1.17) 1.06 (1.00–1.12) 1.12 (1.03–1.22)	Disease recurrence Disease mortality	Stage at diagnosis, age, meat, butter/margarine/lard intake, beer intake, menopausal status
(64)	France	Retrospective cohort	605 80 local recurrences	<i>Post-diagnosis</i> BMI	Continuous	0.92 (0.85–0.99) 1.01 (0.96–1.06)	Local recurrence Distant metastases	Age, axillary nodes, multifocality
(8)	Canada	Prospective cohort	603 112 deaths	<i>Post-diagnosis</i> WHR (quartiles)	>0.848 vs <0.756 <i>Premenopausal</i> <i>Postmenopausal</i>	1.2 (0.4–3.4) 3.3 (1.1–10.4)	Disease mortality	Age, BMI, family history of breast cancer, ER status, stage at diagnosis, systemic treatment
(26)	U.S.	Follow-up of cases from RCT	3385 787 recurrences 595 deaths	<i>Post-diagnosis</i> BMI	30 vs <25 30 vs 18.5–24.9	0.98 (0.80–1.18) 1.20 (0.97–1.49)	Disease free survival Disease mortality	Treatment, age, menopausal status, race, tumor size, ER and PR levels
(7)	International	Follow-up of cases from RCT	6370	<i>Post-diagnosis</i> BMI	30 vs 24.9	1.10 (1.10–1.20)	Disease free survival	ER status, menopausal status, nodal status, tumor size, treatment

Reference	Location	Design	Sample (n)	Time of exposure	Contrast	RR/HR (95% CI)	Outcome	Covariates
(30)	U.S.	Retrospective cohort	1376 246 deaths	Weight at diagnosis (lb)	175 vs <133 All stages	1.60 (0.99–2.56)	Disease mortality	Age, grade, stage, tumor size, lymph node status, ER status
(29)	U.S.	Follow-up of cases (aged 40 years) in a case-control study	717 251 deaths	<i>Pre-diagnosis</i> BMI Weight gain (kg) from age 18 to 1 yr before diagnosis	25 vs <20.4 >10 vs 0	0.76 (0.53–1.07) 0.93 (0.61–1.42)	Disease mortality	Age, stage at diagnosis, physical activity
(62)	Norway	Prospective cohort	1211 471 deaths	<i>Pre-diagnosis</i> BMI (quintiles)	Fifth vs first	1.38 (1.04–1.84)	Disease mortality	Lymph node status, tumor diameter, mean nuclear area
(51)	U.S.	Prospective cohort	5,204 533 deaths 681 recurrences	<i>Pre-diagnosis</i> BMI BMI change (from pre to post diagnosis) in kg/m ²	30 vs 21–22 <i>Premenopausal</i> <i>Postmenopausal</i> 2.0 vs 0; <25 kg/m ² 25 kg/m ²	1.09 (0.80–1.48) 1.0 (0.76–1.31) 2.02 (1.13–3.61) 0.88 (0.61–1.28) 1.90 (1.32–2.72) 0.75 (0.51–1.11)	Disease mortality Disease-free survival Disease mortality Disease mortality	Age, OC use, birth index, menopausal status, age at menopause, HRT use, smoking status, protein intake, tumor size, nodal status, chemotherapy use, tamoxifen use
(57)	Australia	Follow-up of cases in case-control study	1,360 264 distant recurrences	<i>Pre-diagnosis</i> BMI	>30 vs ≤30 <i>Premenopausal</i> <i>Postmenopausal</i>	1.57 (1.11–2.22) 1.50 (1.00–2.26) 2.03 (0.99–4.21)	Distant recurrence	Age, tumor grade, nodal status, PR status
(103)	China	Follow-up of cases in case-control study	1455	<i>Post-diagnosis</i> BMI (quartiles)	25.53 vs <21.23	1.3 (1.0–1.8)	Disease mortality/recurrence	Age at diagnosis, education, menopausal status, tumor-node metastasis

Reference	Location	Design	Sample (n)	Time of exposure	Contrast	RR/HR (95% CI)	Outcome	Covariates
(107)	U.S.	Follow-up of cases in case-control study	3924 1347 deaths	<i>Post-diagnosis</i> BMI Weight change (lbs) from age 18 to adult weight	30 vs 22.99 <i>Premenopausal</i> <i>Postmenopausal</i> 31 vs 0	1.34 (1.09–1.65) 1.38 (1.05–1.80) 1.32 (0.94–1.83) 1.02 (0.82–1.27)	Disease mortality	Age at diagnosis, race, radiation therapy, history of benign breast disease, education, menopausal status, cancer stage, adult BMI
(9)	U.S.	Prospective cohort (includes arm of trial)	3057 333 recurrences	Change in weight from pre-diagnosis to entry Weight gain Weight loss	>10% vs $\pm$ 5% >10% vs $\pm$ 5%	1.0 (0.7–1.3) 1.0 (0.7–1.6)	Disease mortality/recurrence	Stage, age, pre diagnosis BMI, tamoxifen use, treatment, number of positive nodes, PR and ER status
(24)	U.S.	Follow-up of cases from RCT	4077 772 recurrences 624 deaths	<i>Post-diagnosis</i> BMI	35 vs 18.5–24.9 30–34.9 vs 18.5–24.9 35 vs 18.5–24.9 30–34.9 vs 18.5–24.9	1.04 (0.80–1.35) 1.06 (0.86–1.32) 1.13 (0.85–1.49) 1.02 (0.80–1.31)	Disease recurrence Disease recurrence Disease mortality Disease mortality	Treatment, tumor size, age, race
(16)	U.S.	Follow-up of cases in case-control study	1508 128 deaths	<i>Pre-diagnosis</i> BMI Weight (kg) Weight change (kg) <i>Premenopausal</i>	30 vs <25 <i>Premenopausal</i> <i>Postmenopausal</i> 72.6 vs <56.2	2.85 (1.30–6.24) 1.88 (1.04–3.34) 2.41 (0.91–6.39)	Disease mortality	Age at diagnosis, hypertension Age at diagnosis, weight at 20 yrs, and hypertension

Reference	Location	Design	Sample (n)	Time of exposure	Contrast	RR/HR (95% CI)	Outcome	Covariates
				20 yrs to 1 yr before diagnosis	>15.9 vs ± 3	2.09 (0.80–5.48)		Age at diagnosis, weight at age 20, hypertension
				<i>Postmenopausal</i>				
				20 yrs to 1 yr before diagnosis	>22.2 vs ± 3	1.97 (0.74–5.27)		Further adjusted for weight change from 50 to 1 yr before diagnosis
				20 to 50 yrs before diagnosis	>14.1 vs ± 3	1.66 (0.40–6.84)		Weight at age 50, weight change from age 20 to 1 year before diagnosis, hypertension
(87)	U.S.	Prospective cohort	533 (aged 65 yrs) 45 deaths	<i>Post-diagnosis</i> BMI	34.0 vs 22.6	4.93 (1.12–21.70)	Disease mortality	Smoking status, stage, ER status
				Age 65	27.3 vs 22.6	1.93 (1.05–3.56)		
				Age 85	34.0 vs 22.6	0.30 (0.08–1.09)		
					27.3 vs 22.6	0.61 (0.35–1.04)		
(10)	U.S.	Prospective cohort	1,689 207 events for recurrence 90 mortality events	<i>Pre-diagnosis</i> BMI	30 vs <25	1.3 (0.9–1.9)	Disease recurrence	Stage, age, tamoxifen use, treatment, number of positive nodes, progesterone & estrogen receptor status, smoking history, MET hrs per week of non-sedentary activities
				<i>Post-diagnosis</i> BMI	30 vs <25	1.6 (0.9–2.7)	Disease mortality	
					30 vs <25	1.0 (0.7–1.4)	Disease recurrence	
				Weight gain	30 vs <25	1.2 (0.7–2.1)	Disease mortality	
				Weight loss	10% vs $\pm 5\%$	0.8 (0.5–1.2)	Disease recurrence	
					10% vs $\pm 5\%$	1.7 (1.0–2.6)	Disease recurrence	
(18)	Italy	Follow up of cases in case-control study	1,453	<i>Pre-diagnosis</i> BMI	30 vs <25	1.38 (1.02–1.86)	Disease mortality	Region of residence, age at and year of diagnosis, TNM

Reference	Location	Design	Sample (n)	Time of exposure	Contrast	RR/HR (95% CI)	Outcome	Covariates
			398 deaths	Increase in BMI from age 30 to diagnosis	5.0 vs <1.5	1.38 (1.05–1.83)		stage and ER/PR status
(21)	U.S.	Follow-up of cases from RCT	602 325 recurrences	<i>Post-diagnosis</i> BMI	30 vs 18.5–24.9	1.42 (1.05–1.92)	Recurrence-free survival	Year of diagnosis, age, number of positive lymph nodes, number of lymph nodes removed, menopausal status, pathologic complete response, chemotherapy, BC type
(72)	Korea	Retrospective cohort	24,698	<i>Post-diagnosis</i> BMI	25 vs 18.5–24.9	0.94 (0.72–1.23) 0.90 (0.66–1.23) 0.87 (0.52–1.39)	Disease-free survival Distant metastases free survival Locoregional recurrence-free survival	Age, tumor size
(75)	U.S.	Prospective cohort	3,993 121 deaths	<i>Pre-diagnosis</i> BMI <i>Post-diagnosis</i> BMI Weight change since diagnosis	30 vs 18.5–24.9 30 vs 18.5–24.9 5 kg increase 5 kg decrease >10 vs $\pm$ 2	1.42 (0.86–2.36) 2.28 (1.43–3.64) 1.13 (1.03–1.25) 0.79 (0.42–1.47) 1.78 (1.01–3.14)	Disease mortality	Age, state, time between diagnosis and follow up interview, family history of BC, smoking, total recreational physical activity at follow up, menopausal status, stage
(95)	Sweden	Follow-up of cases in case-control study	2640 354 BC deaths	<i>Pre-diagnosis</i> BMI	>30 vs <25 All women	1.2 (0.9–1.6)	Disease mortality	Age at diagnosis, current alcohol intake, tumor size, lymph node positivity
(14)	China	Prospective cohort	5,042	<i>Pre-diagnosis</i> BMI	30 vs <18.5–24.9	1.39 (0.98–1.97)	Disease mortality/recurrence	Age, education, income, marital status,

Reference	Location	Design	Sample (n)	Time of exposure	Contrast	RR/HR (95% CI)	Outcome	Covariates
			534 deaths	<p><i>At diagnosis</i> BMI</p> <p><i>Post-diagnosis</i> BMI</p> <p>Weight change(kg) Pre-diagnosis to 6 months post-diagnosis</p> <p>Pre-diagnosis to 18 months post-diagnosis</p> <p>Diagnosis to 18 months post-diagnosis</p>	<p>30 vs <18.5-24.9</p> <p>30 vs <18.5- 24.9</p> <p>5 vs $\pm$1</p> <p>5 vs $\pm$1</p> <p>5 vs $\pm$1</p>	<p>1.44 (1.02–2.03)</p> <p>1.49 (1.08–2.06)</p> <p>1.31 (0.97–1.75)</p> <p>1.90 (1.23–2.93)</p> <p>1.30 (0.88–1.92)</p>		comorbidity, exercise participation, intake of meats, cruciferous vegetables, & soy protein, time interval from diagnosis to study enrollment, menopausal status, menopausal symptoms, surgery, chemotherapy, radiotherapy, immunotherapy, tamoxifen use, tumor-node metastasis stage, ER/PR receptor status
(22)	International	Retrospective analysis from RCT	2,887 368 deaths	<i>Post-diagnosis</i> BMI	30–34.9 vs 18.5–24.9	1.20 (p=0.04)	Disease mortality/recurrence	Hormone receptor status, age, menopausal status, tumor size, number of positive lymph nodes
(45)	UK	Prospective cohort	2,298	<i>Post-diagnosis</i> BMI	<p>30 vs <30</p> <p>Continuous</p>	<p>1.43 (1.12–1.83)</p> <p>1.02 (1.0–1.04)</p>	<p>Disease-free survival</p>	Age, tumor size, tumor grade, lymph node status, vascular invasion, operation, adjuvant treatment, year of diagnosis
(98)	International	Retrospective analysis from RCT	4939 878 recurrences	<i>Post-diagnosis</i> BMI (only postmenopausal)	<p>>35 vs <23</p> <p>30–35 vs <23</p> <p>>35 vs <23</p> <p>30–35 vs <23</p>	<p>1.55 (1.10–2.19)</p> <p>1.21 (1.03–1.86)</p> <p>1.39 (1.06–1.82)</p> <p>1.14 (0.91–1.44)</p>	<p>Disease mortality</p> <p>Disease recurrence</p>	Age, region, nodal status, chemotherapy, radiotherapy, mastectomy, tumor size and grade
(31)	Denmark	Retrospective analysis from RCT	18,967	<i>Post-diagnosis</i>	>30 vs <25	0.74 (0.46–1.18)	5–10 yr locoregional recurrence	Age, menopausal status, tumor

Reference	Location	Design	Sample (n)	Time of exposure	Contrast	RR/HR (95% CI)	Outcome	Covariates
			1544 locoregional recurrence events 3,277 distant metastases	BMI		1.46 (1.11–1.92) 1.38 (1.11–1.71)	5–10 yr distant metastases Disease mortality	size, nodal status, deep fascia invasion, histologic type and grade, ER status, protocol year, systemic therapy

Abbreviations: BC, breast cancer; BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; RCT, randomized controlled trial.

Table 2
Studies evaluating body mass index (BMI) and colorectal cancer mortality and disease-free survival (n=8)

Reference	Location	Design	Sample (n)	Time of exposure	Contrast	HR/RR (95% CI) or summary of results	Outcome	Covariates considered
(68)	U.S.	Follow-up of cases in RCT	3,759 colon cancer patients stages II-III; 12,899 recurrences	<i>Post-diagnosis</i> BMI measured on day 1 of chemotherapy	30 vs. 21-24.9 <i>All subjects</i> <i>Females</i> <i>Males</i>	1.11 (0.94-1.30) 1.24 (0.98-1.59) 0.98 (0.77-1.15)	Recurrence	Age, race, baseline performance status, bowel obstruction, bowel perforation, Duke stage of disease, presence of peritoneal implants, predominant macroscopic pathologic feature and completion chemotherapy
(70)	U.S.	Follow-up of cases in RCT	1688 RC patients stages II-III	<i>Post-diagnosis</i> BMI measured at start of chemotherapy	30 vs. 20-24.9 <i>All subjects</i> <i>Females</i> <i>Males</i>	1.31 (0.91-1.88) 1.01 (0.57-1.81) 1.61 (1.00-2.59)	Local recurrence	Age, race, baseline performance status, bowel obstruction, extent of bowel-wall invasion, number of lymph nodes and operation type extent of difference
(25)	U.S.	Prospective Cohort	4288 with Dukes B and C colon cancer 1159 CC deaths 1286 CC recurrences or secondary primary tumors	<i>Post-diagnosis</i> BMI measured on day 1 of chemotherapy	30-34.9 vs. 25 >35 vs. 18.5-24.9	1.08(0.90-1.30) 1.04(0.88-1.24) 1.06(0.93-1.21) 1.36 (1.06-1.73) 1.38 (1.10-1.73) 1.27 (1.05-1.53)	CC mortality Colon cancer events Disease-free survival CC mortality Colon cancer events Disease free survival	Age, gender, race, performance status, number of positive lymph nodes, presence of bowel obstruction and treatment
(27)	U.S.	Follow-up of cases in a case-control study	633 CRC females 147 CRC deaths	<i>Pre-diagnosis</i> Self-reported BMI	30 vs 20-24.9	2.1 (1.1-3.8) 0.6 (0.2-1.6) 1.5 (0.9-2.6)	CC mortality RC mortality Colorectal mortality	Age, stage of cancer, postmenopausal hormone use, smoking
(41)	Australia	Prospective Cohort	526 CRC patients stages I-IV 181 CRC deaths	<i>Pre-diagnosis</i> BMI	BMI per 5 kg/m ²	1.15 (0.98-1.35)	CRC specific mortality	Age, gender, cancer stage

Reference	Location	Design	Sample (n)	Time of exposure	Contrast	HR/RR (95% CI) or summary of results	Outcome	Covariates considered
(69)	U.S.	Follow up of cases in a RCT	1053 CRC pts, stage III treated 261 deaths 369 recurrences and deaths 338 recurrences	<i>Post-diagnosis</i> Self-reported BMI	35 vs 21–24.9 30–34.9 vs 21–24.9 35 vs 21–24.9 30–34.9 vs 21–24.9	1.24 (0.84–1.83) 1.00 (0.72–1.40) 1.27 (0.88–1.89) 0.97 (0.69–1.37)	Disease free survival Recurrence free survival	Age, gender, invasion through bowel wall, number of positive lymph nodes, clinical perforation at time of surgery, bowel obstruction at time of surgery, baseline performance status, treatment group, time between questionnaires, time varying BMI, smoking status, physical activity
(85)	U.S.	Prospective Cohort	1,096 CC (females) 289 CC deaths	<i>Pre-diagnosis</i> BMI	30 vs 18.5–24.9	1.32 (0.95–1.82)	CC mortality	Age at diagnosis, stage, education, smoking
(102)	U.S.	Prospective Cohort within RCT	4,381 participants with stage II and III CC 1,833 deaths 1,585 recurrences	<i>Post-diagnosis</i> BMI	>35 vs 20–24.9 30–34 vs 20–24.9	1.23 (1.01–1.49) 1.08 (0.94–1.25) HR not shown for multivariable analyses; p=0.03	Disease free survival	Univariate Age, stage, treatment, gender

Abbreviations: BMI, body mass index; CC, colon cancer; *CRC, colorectal cancer; *RC, rectal cancer; RCT, randomized controlled trial.

Table 3

Studies evaluating body mass index (BMI) and prostate cancer survival (n=6)

Reference	Location	Design	Sample (n)	Time of exposure	Contrast	HR/RR (95% CI)	Outcome	Covariates considered
(37)	U.S.	Follow-up of cases in a case-control study	752 50 PCa deaths	<i>Pre-diagnosis</i> self-reported BMI	30 vs. <25	2.64 (1.18–5.92)	PCa mortality	Age, race, Gleason score, smoking status, stage at diagnosis, primary treatment
(100)	U.S.	Prospective cohort	5,313 50 PCa deaths	<i>Post-diagnosis</i> BMI	Continuous	1.02 (0.97–1.07)	PCa mortality	Gleason score at prostatectomy, serum PSA, surgical margin, seminal vesicle invasion, adjuvant treatment
(28)	U.S.	Follow-up of cases in RCT	788 169 PCa deaths	<i>Post-diagnosis</i> BMI	30 vs. <25	1.64 (1.01–2.66)	PCa mortality	Age, race, treatment arm, prostatectomy, nodal involvement, Gleason score, stage, primary treatment
(58)	U.S.	Follow-up of cases in RCT	2546 281 PCa deaths	<i>Pre-diagnosis</i> BMI	30 vs < 25 Continuous	1.95 (1.17–3.23) 1.07 (1.02–1.12)	PCa mortality	Age, baseline smoking status, time between BMI measurement and prostate cancer diagnosis, stage, Gleason grade
(19)	U.S.	Prospective cohort	7,274 220 PCa deaths	<i>Post-diagnosis</i> BMI	30–34.99 vs. <25 35 vs. <25	0.9 (0.6–1.3) 0.5 (0.2–1.2)	PCa mortality	Age, clinical risk, treatment, diabetes
(104)	The Netherlands	Retrospective cohort	1530 61 PCa deaths	<i>Post-diagnosis</i> BMI	30 vs. <25	1.46 (0.50–4.28)	PCa mortality	Age, stage, grade, preoperative PSA, pelvic lymph node dissection, treatment period, number of seeds

Abbreviations: BMI, body mass index; PCa, prostate cancer; PSA, prostate-specific antigen; RCT, randomized controlled trial