Obesity and cancer: mechanistic insights from transdisciplinary studies

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Abstract

Obesity is associated with a range of health outcomes that are of clinical and public health significance, including cancer. Herein, we summarize epidemiologic and preclinical evidence for an association between obesity and increased risk of breast and prostate cancer incidence and mortality. Moreover, we describe data from observational studies of weight change in humans and from calorie restriction studies in mouse models which support a potential role for weight loss in counteracting tumor-promoting properties of obesity in breast and prostate cancers. Given that weight loss is challenging to achieve and maintain, we also consider evidence linking treatments for obesity-associated co-morbidities, including metformin, statins and non-steroidal anti-inflammatory drugs, with reduced breast and prostate cancer incidence and mortality. Finally, we highlight several challenges that should be considered when conducting epidemiologic and preclinical research in the area of obesity and cancer, including the measurement of obesity in population-based studies, the timing of obesity and weight change in relation to tumor latency and cancer diagnosis, and the heterogeneous nature of obesity and its associated co-morbidities. Given that obesity is a complex trait, comprised of behavioral, epidemiologic and molecular/metabolic factors, we argue that a transdisciplinary approach is the key to understanding the mechanisms linking obesity and cancer. As such, this review highlights the critical need to integrate evidence from both epidemiologic and preclinical studies to gain insight into both biologic and non-biologic mechanisms contributing to the obesity-cancer link.

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1. Introduction

Cancer is predicted to overtake heart disease as the leading cause of death across all age groups in the US by 2030, translating to a 45% increase in the number of cancer diagnoses in the next 15 years (American Society of Clinical Oncology 2014). Global obesity prevalence has been increasing by approximately half a body mass index (BMI) unit per decade over the past three decades, resulting in over 600 million adults worldwide with a BMI of 30 kg/m^2 or greater (Finucane, et al. 2011; Stevens, et al. 2012). With more than one in three US adults classified as obese, the prevalence of obesity in the US is currently the highest in the Western world (Finucane et al. 2011; Ogden, et al. 2014).

Obesity is associated with increased risk of a variety of different cancer types (World Cancer Research Fund 2007). Of these obesity-associated cancer types, almost 13% of incident cases worldwide, and approximately 20% of incident cases in Europe and North America, are attributable to obesity (Arnold, et al. 2014). Furthermore, it is estimated that one quarter of these cases could have been avoided had the worldwide obesity prevalence not approximately doubled since 1980 (Arnold, et al. 2014). Overweight and obesity also drive cancer progression, and have been estimated to account for 14% of all cancer deaths in men and 20% in women in the United States (Calle, et al. 2003), while approximately 6% of cancer deaths around the same time period in Europe were attributable to obesity (Banegas, et al. 2003).

Cancers of the breast and prostate are among the most commonly diagnosed and among the leading causes of cancer deaths in women and men, respectively, both in the US and worldwide (Jemal, et al. 2011; Siegel, et al. 2013). Therefore, understanding mechanisms linking obesity and risk of these common tumor types will be important for cancer prevention efforts worldwide. In addition, of over 11 million US individuals living with cancer, survivors of breast cancer constitute the largest group (22%), followed by survivors of prostate cancer (19%) (Centers for Disease Control & Prevention 2011). Therefore, understanding mechanisms linking obesity and cancer progression in these common tumor types has great importance for a large proportion of cancer survivors, and will likely also benefit survivors of other obesity-associated cancer types. Molecular mechanisms linking obesity and cancer have been reviewed in depth elsewhere (Allott, et al. 2013b; Ford, et al. 2013a; Lashinger, et al. 2014a). As such, this review adopts a transdisciplinary approach, summarizing findings from both epidemiologic and preclinical studies (Figure 1), in addition to examining evidence for the modifiable nature of obesity and related co-morbidities through weight loss and pharmacologic interventions in both humans and mouse models. Finally, we consider how a transdisciplinary approach can minimize the weaknesses and maximize the strengths of each discipline, enabling a deeper understanding of mechanisms linking obesity and cancer.

2. Transdisciplinary insights into associations between obesity and cancer

i. Obesity and breast cancer

The association between obesity and breast cancer risk is complex, varying by menopausal status and by breast cancer subtype. Obesity is associated with reduced breast cancer

incidence in premenopausal women (World Cancer Research Fund 2007), but increased breast cancer incidence in postmenopausal women (Munsell, et al. 2014; World Cancer Research Fund 2007), although the association with postmenopausal breast cancer is attenuated in women using hormone replacement therapy (Munsell et al. 2014). While these contrasting associations by menopausal status are consistently reported, differences in these associations by hormone receptor status are less well understood. Within postmenopausal breast cancers, there is a suggestion that the association with obesity is strongest among hormone receptor-positive cases (Althuis, et al. 2004; Canchola, et al. 2012; Rosenberg, et al. 2006; Suzuki, et al. 2009), although other studies did not find differences in these associations by breast cancer subtype (Millikan, et al. 2008; Phipps, et al. 2008; Yang, et al. 2011). Several studies have reported that, although obesity is a protective factor for total premenopausal breast cancer, it is associated with increased risk of triple negative and basal-like disease in premenopausal women (Gaudet, et al. 2011; Millikan et al. 2008; Yang et al. 2011). Interestingly, some evidence suggests that obesity may be a risk factor for basal-like breast cancer regardless of menopausal status (Millikan et al. 2008), suggesting a role for non-hormonal mechanisms in basal-like breast cancer pathogenesis.

While the association between obesity and breast cancer risk differs by menopausal status, obesity is associated with increased risk of breast cancer recurrence and mortality in both pre and postmenopausal women (Chan, et al. 2014; Niraula, et al. 2012). While several studies have suggested that this association may be stronger among women with hormone receptor-positive tumors (Azrad and Demark-Wahnefried 2014; Jiralerspong, et al. 2013; Sparano, et al. 2012; Tait, et al. 2014), others reported no difference in the association between obesity and breast cancer-specific mortality by subtype (Niraula et al. 2012; Phipps et al. 2008). However, partial availability of subtype data and lower numbers of patients with rarer breast cancer subtypes is a limitation for many studies (Althuis et al. 2004). Given evidence for etiologic heterogeneity of breast cancer, understanding the obesity-breast cancer link in humans requires large, well-annotated studies with sufficient power to conduct stratified analysis both by menopausal status and subtype.

The recognition of breast cancer as a heterogeneous disease has led to the characterization of mouse models which reflect human breast cancer subtypes (Herschkowitz, et al. 2007). One particular challenge of preclinical models of breast cancer is that estrogen receptor (ER) is weakly expressed in most mouse mammary tumors, particularly in genetically-engineered mice, and thus murine models of hormone receptor-positive breast cancer may not be fully representative of human luminal breast cancer (Borowsky 2011; Herschkowitz et al. 2007). Nonetheless, diet-induced obesity has been demonstrated to drive tumor growth in a variety of mouse models with both luminal (Ford, et al. 2013b; Pape-Ansorge, et al. 2002) and basal-like tumor characteristics (Dogan, et al. 2007; Dunlap, et al. 2012; Giles, et al. 2012; Hakkak, et al. 2007; Nogueira, et al. 2012; Sundaram, et al. 2013), lending support to epidemiologic observations. In contrast, there is little preclinical support for links between obesity and luminal B or HER-2 breast cancer subtypes (Cleary, et al. 2004; Ford, et al. 2013b), although the degree to which these models are representative of these human subtypes is unclear. Finally, one study showed that diet-induced obesity enhanced the growth of luminal-like tumors in ovariectomized mice, but not in mice with intact ovaries (Nunez, et al. 2008), suggesting that the relationship between obesity and postmenopausal

luminal breast cancer should be tested in ovariectomized mice in order to model the human postmenopausal environment. However, given epidemiologic evidence supporting an association between obesity and basal-like breast cancer regardless of menopausal status, the relevance of ovariectomization to study the impact of diet-induced obesity on basal-like breast cancer in mouse models is less clear.

ii. Obesity and prostate cancer

Although individual studies are conflicted regarding the association between obesity and prostate cancer risk, a number of large meta-analyses have reported that obesity is associated with a modestly elevated total prostate cancer incidence (Bergstrom, et al. 2001; Hu, et al. 2014; MacInnis and English 2006; Renehan, et al. 2008). One meta-analysis demonstrated that findings from the individual contributing studies differed by geographic region (Renehan et al. 2008), thereby offering insight into these somewhat conflicted results. Prostate specific antigen (PSA) levels are reduced in obese men via hemodilution (Banez, et al. 2007), thereby lowering the likelihood of a PSA-driven biopsy and giving rise to an obesity-associated detection bias. This bias becomes apparent when comparing the results of US studies where PSA screening is widespread, with the results of European studies where PSA screening is less common (Renehan et al. 2008). In the US, where prostate biopsies are largely driven by PSA screening, obese men have a reduced chance of undergoing biopsy compared to normal weight men, leading to the detection of fewer cancers in obese individuals and biasing the association between obesity and prostate cancer towards the null. In countries with lower PSA screening rates, such as Europe and Australia, this detection bias is reduced and meta-analysis of studies from these regions demonstrates a positive association between obesity and prostate cancer risk (Renehan et al. 2008). These data highlight the importance of considering how the association between obesity and prostate cancer risk is impacted by mode of cancer detection, particularly in the context of changing PSA screening recommendations in the US (Moyer and U.S. Preventative Services Task Force 2012).

While the association between obesity and total prostate cancer is complicated by obesity-associated detection bias, there is consistent and convincing evidence for an association between obesity and elevated risk of aggressive prostate cancer (Rodriguez, et al. 2007; Zhang, et al. 2015). Furthermore, multiple large studies, both before and after the introduction of widespread PSA screening in the US, demonstrated an association between obesity and increased prostate cancer-specific mortality (Andersson, et al. 1997; Cao and Ma 2011; Rodriguez, et al. 2001; Wright, et al. 2007; Zhang et al. 2015), indicating that obesity-associated detection bias does not completely explain the association between obesity and prostate cancer, but that biologic mechanisms must also play a role.

Consistent with epidemiologic evidence for an association between obesity and tumor aggressiveness and progression, tumor growth in mouse models of prostate cancer has been shown to be responsive to obesity. A number of studies have demonstrated a role for diet-induced obesity in promoting prostate tumor growth in the transgenic adenocarcinoma of the prostate (TRAMP) mouse model (Bonorden, et al. 2012; Llaverias, et al. 2010). In addition, diet-induced obesity reduced tumor latency in the Hi-Myc mouse model, via increased Akt/

mTOR signaling (Blando, et al. 2011; Kobayashi, et al. 2008), and promoted tumor progression in a transgenic mouse model with PTEN haploinsufficiency, via increased inflammatory and insulin signaling pathways (Liu, et al. 2015). These transgenic models may have relevance to human prostate cancer given that Myc copy number is amplified in up to one third of human prostate cancers (Ellwood-Yen, et al. 2003) and PTEN loss is the most common genetic alteration in human prostate cancer (Wang, et al. 2003).

3. Non-biologic mechanisms contributing to the obesity - cancer link

i. Obesity and cancer screening

Evidence suggests that obesity-associated screening and detection biases may act to delay cancer diagnosis, thereby increasing cancer-specific mortality in obese patients (Figure 2). Obese individuals may be less likely to participate in screening programs which could contribute to delayed cancer diagnosis, an association shown to be modified by the type of screening test, by race and by gender (Fagan, et al. 2011). Indeed, mammography screening rates are reduced by as much as 10% in obese (BMI $\geq$ 30 kg/m^2) and 20% in morbidly obese (BMI $\geq$ 40 kg/m^2) women (Maruthur, et al. 2009) and while the reasons for reduced participation in cancer screening are not completely understood, they may include modesty, pain, and/or competing healthcare demands (Friedman, et al. 2012).

In contrast to associations with breast cancer screening, an inverse association between obesity and PSA screening frequency has been reported in prostate cancer, with obese men being screened more frequently than their normal weight counterparts (Scales, et al. 2007). However, obesity is associated with reduced likelihood of prostate cancer diagnosis in a screened population despite higher PSA screening frequency in obese men, suggesting that obesity may decrease screening effectiveness in some cancer types. In obese prostate cancer patients, their larger body size and bigger prostate make conducting a digital rectal exam more challenging (Chu, et al. 2011), and a large prostate may reduce the likelihood of finding the cancer at biopsy (Freedland, et al. 2006). This is also true for other cancer types; mammography is anecdotally more difficult in obese patients (Amy, et al. 2006), potentially delaying cancer diagnosis even in screened obese individuals. Indeed, obesity has been associated with higher stage at breast cancer diagnosis (Cui, et al. 2002), suggesting that obese women may be diagnosed later in the course of their disease. However, another study reported this finding regardless of mammography screening frequency, suggesting that the association between obesity and high stage breast cancer may not simply be a result of lower screening rates in this population (Kerlikowske, et al. 2008), but that biologic mechanisms must also play a role.

Finally, the larger blood volume in obese individuals has been associated with biomarker hemodilution, as has been suggested in PSA-detected prostate cancer (Banez et al. 2007). Several studies have estimated that PSA levels are reduced by approximately 15% in cancer-free morbidly obese (BMI $\geq$ 35 kg/m^2) men, while PSA mass (i.e. the absolute quantity of PSA in the blood) is not associated with obesity status (Grubb, et al. 2009; Rundle and Neugut 2009). Lower biomarker levels in obesity reduce the likelihood of reaching biopsy thresholds, potentially contributing to delayed diagnosis in obese individuals.

ii. Obesity and cancer treatment

In addition to biologic mechanisms [reviewed in (Lashinger, et al. 2014b)], non-biologic factors also contribute to reduced treatment efficacy in obese patients (Figure 2). There is considerable evidence to suggest that obese cancer patients are undertreated with systemic therapies (Lyman and Sparreboom 2013), and this may negatively impact cancer outcomes. Traditionally, chemotherapy dosing is based upon the body surface area (BSA) of the patient. However, there is uncertainty regarding dosing of obese patients and evidence that dose reduction occurs in this population, either because an idealized body weight is used to calculate BSA, or because BSA is arbitrarily capped due to toxicity concerns (Lyman, et al. 2003). Current clinical guidelines for chemotherapy dosing in obese patients indicate that weight-based chemotherapy doses should be given and that dose should not be reduced for obese patients (Griggs, et al. 2012). As such, it is recommended that any modifications to dose due to toxicity concerns or presence of co-morbidities should be made independent of the patient's obesity status (Lyman and Sparreboom 2013).

In prostate cancer, obesity is associated with increased daily prostate shift, rendering external beam radiation treatment more technically challenging, and potentially contributing to increased rates of treatment failure in obese patients (Merrick, et al. 2007). Technical difficulties applying the adequate radiation dose to the correct area in obese patients has also been suggested in breast cancer (Carmichael and Bates 2004). In addition to these potential difficulties with radiation therapy, obese patients may also be less likely to make good surgical candidates. In prostate cancer, obesity has been shown to be associated with capsular incision, reflecting a less-than-ideal operation (Freedland, et al. 2005). However, even when focusing solely on patients with organ-confined disease and negative surgical margins, obesity remains associated with biochemical recurrence following radical prostatectomy, implying that obesity is associated with disease progression in prostate cancer through mechanisms other than how it may affect surgical technique (Freedland, et al. 2004).

Obesity and related co-morbidities are associated with increased risk of adverse treatment effects, which may impact the treatment plan (Schmitz, et al. 2013). In breast cancer, obesity has been associated with a higher risk of lymphedema, in addition to other treatment-related side effects (Togawa, et al. 2014). Obese, diabetic breast cancer patients undergoing chemotherapy have increased likelihood of side effects including infection and chemotherapy-related toxicity (Srokowski, et al. 2009). In addition, cytotoxic therapy has been associated with treatment-related weight gain and metabolic syndrome in breast cancer patients (Bicakli, et al. 2014; Makari-Judson, et al. 2014), potentially exacerbating these aforementioned side effects. In prostate cancer, obesity is associated with weight gain and increased risk of diabetes following androgen deprivation therapy (Keto, et al. 2011; Tsai, et al. 2014), particularly among older men (Morgans, et al. 2014). Given that more men diagnosed with prostate cancer die from cardiovascular disease than from prostate cancer (Allott et al. 2013b), this relationship has important implications for prostate cancer survivors.

Finally, excess body weight has been linked to altered metabolism of cytotoxic drugs and therapies, potentially via a number of mechanisms including altered levels of circulating

growth factors, hormones and cytokines (Litton, et al. 2008; Rodvold, et al. 1988). Despite evidence that aromatase inhibitors may not be as efficacious in obese breast cancer patients (Azrad and Demark-Wahnefried 2014; Ioannides, et al. 2014; Wolters, et al. 2012), standard doses are given irrespective of BSA or body size (Goodwin and Pritchard 2010). In contrast, response to tamoxifen has not been shown to differ by obesity status (Wolters et al. 2012), and no differences in ER-positive breast cancer recurrence rates by obesity status have been reported following tamoxifen treatment (Dignam, et al. 2003). Finally, one trial suggested that obese breast cancer patients treated with chemotherapy had reduced disease-free survival relative to normal weight patients, even after controlling for other prognostic factors (de Azambuja, et al. 2010). In prostate cancer, obesity at the time of androgen deprivation therapy is associated with increased risk of castrate-resistant prostate cancer, metastasis, and prostate cancer-specific mortality (Keto et al. 2011). Although the exact explanation for this is unclear, one study found that testosterone levels in obese men on androgen deprivation therapy were higher, suggesting inadequate testosterone suppression (Smith 2007). It has been hypothesized that this may be because the amount of gonadotropin-releasing hormone analogue given is the same regardless of BSA, and thus obese men may be under dosed. However, while these non-biological factors must be considered, they cannot completely explain the association between obesity and cancer mortality, and biologic mechanisms also contribute (Lashinger et al. 2014b).

4. Obesity and related co-morbidities as modifiable lifestyle factors

i. Weight gain and loss

Evidence for the association between obesity and cancer is substantiated by studies showing that weight change can impact both risk and survival for obesity-associated cancers (Figure 3). Bariatric procedures to cause weight loss have been associated with reduced risk of obesity-associated cancer types and a 40-50% decrease in cancer-specific mortality across cancer types (Adams, et al. 2009; Sjostrom, et al. 2007), suggesting that weight loss may be an effective chemopreventive strategy in obese individuals (Ashrafian, et al. 2011). Interestingly, one prospective intervention trial suggested that bariatric procedures may be more effective at decreasing cancer risk in women, compared to men (Sjostrom, et al. 2009), although these results should be interpreted with caution given the smaller sample size of males and mean follow-up time of only one decade, which may not be a long enough latency period for certain cancer types to manifest (Renehan 2009). Aside from these studies of bariatric patients, the majority of evidence supporting a role for weight change in breast cancer incidence and mortality comes from secondary analyses of observational studies. Of note, the most common pattern of weight change over time is consistent weight gain throughout adulthood (Harvie, et al. 2005), and therefore statistical power to study the impact of weight loss is often limited.

Adult weight gain is associated with increased risk of postmenopausal breast cancer (Eliassen, et al. 2006), with a suggestion of a stronger association for hormone receptor-positive breast cancer (Eliassen et al. 2006; Vrieling, et al. 2010). Furthermore, adult weight gain prior to diagnosis is associated with increased mortality from postmenopausal breast cancer (Cleveland, et al. 2007). Conversely, weight loss during adulthood, whether before or

after menopause, has been associated with decreased risk of postmenopausal breast cancer (Eliassen et al. 2006; Harvie et al. 2005), again with the strongest inverse associations for hormone receptor-positive breast cancer (Eliassen et al. 2006). While clinical trials to formally examine the impact of weight loss on breast cancer-specific mortality have not yet been conducted, two trials in breast cancer survivors reported that weight loss of >10% of body mass can be achieved in this population (Befort, et al. 2012; Goodwin, et al. 2014). Furthermore, a weight loss intervention in cancer-free postmenopausal women suggested that 10% weight loss is sufficient to positively impact biomarker levels associated with breast cancer in both serum and benign breast tissue (Fabian, et al. 2013), indicating that such an intervention may be both feasible and worthwhile (Irwin 2014).

Evidence from mouse models of breast cancer showing that weight loss impacts tumor growth supports these epidemiologic data. Weight loss can be achieved in mouse models by calorie restriction (CR), a 20-40% reduction in total energy intake relative to a control group fed *ad libitum*, arguably one of the most potent dietary regimens for suppressing carcinogenesis (Hursting, et al. 2010). Despite the suggestion of stronger epidemiologic associations between weight change and hormone receptor-positive breast cancer, CR slows tumor growth in mouse models regardless of tumor subtype (Dunlap et al. 2012; Ford et al. 2013b; Mizuno, et al. 2013; Nogueira et al. 2012; Pape-Ansorge et al. 2002), providing rationale to study the impact of weight loss across breast cancer subtypes in humans. Mechanistic insights from these models have highlighted Akt/mTOR signaling and the insulin/insulin-like growth factor (IGF) 1 axis as two pro-tumor pathways upregulated by obesity and reversed by CR (Hursting et al. 2010). Interestingly, a protective effect of intermittent CR on tumor growth has also been reported (Rogozina, et al. 2013), and this dietary regimen may be more feasible and appealing to humans. While the majority of preclinical studies randomize mice to CR from the outset, two preclinical studies have specifically tested the impact of diet-induced obesity followed by weight loss, by incorporating a diet switch during the intervention period. Interestingly, these studies reported contrasting findings, with one reporting that weight loss reversed the tumor-promoting effect of obesity (Sundaram, et al. 2014b), and the other reporting the weight loss did not impact obesity-fueled tumor growth (De Angel, et al. 2013). Key differences between studies included the degree of obesity attained by the mice and the timing and duration of weight loss, in addition to the use of two different mouse models of basal-like breast cancer, one xenograft (De Angel et al. 2013) and the other transgenic (Sundaram et al. 2014b). Discrepant findings such as these may shed light on mechanisms linking weight loss and breast cancer, in addition to informing future study design in both preclinical mouse models and humans.

Retrospective analyses of large cohort studies have also revealed inverse associations between weight loss and prostate cancer incidence and mortality. Relative to weight maintenance, adult weight gain is associated with increased risk of aggressive prostate cancer (Bassett, et al. 2011), while adult weight loss is associated with reduced risk of aggressive prostate cancer (Rodriguez et al. 2007). Furthermore, some large prospective cohort studies have reported that weight gain in adulthood is associated with increased prostate cancer-specific mortality (Bassett et al. 2011; Wright et al. 2007), although others

reported no association between adult weight change and prostate cancer-specific mortality (Chamberlain, et al. 2011; Moller, et al. 2013). Studies focused on weight change within the decade of prostate cancer diagnosis report more consistent findings, with weight gain in the five year time period preceding diagnosis associated with increased risk of recurrence (Joshu, et al. 2011; Whitley, et al. 2011), and weight gain in the five year time period following diagnosis associated with increased risk of prostate cancer-specific mortality (Bonn, et al. 2014).

While evidence for a role for weight loss in counteracting tumor growth in mouse models of prostate cancer is relatively sparse, a tumor-inhibitory effect of CR has been demonstrated via reduced insulin/IGF1 levels and increased tumor apoptosis in a xenograft mouse model (Galet, et al. 2013), although this effect has not been reported in all xenograft models (Buschemeyer, et al. 2010; Thomas, et al. 2010). In addition, one study demonstrated that CR slowed progression to adenocarcinoma in the Hi-Myc transgenic mouse model of prostate cancer, via reduced prostate inflammation and inhibition of Akt/mTOR signaling (Blando et al. 2011). CR has also been demonstrated to impact tumor growth in the TRAMP model, with intermittent CR having a greater impact than chronic CR (Bonorden, et al. 2009), although a role for intermittent CR has not been supported by other prostate cancer studies (Buschemeyer et al. 2010; Thomas et al. 2010).

Given the challenges surrounding compliance with CR and maintenance of weight loss in humans, alternative strategies are also worth exploring. Intermittent CR is one such strategy, and while one randomized weight loss trial in women showed that both intermittent and chronic CR caused weight loss and improved insulin sensitivity and cytokine profile (Harvie, et al. 2011), avoiding weight gain may remain the most sensible approach both for general health in addition to chemoprevention (Thompson and McTiernan 2011). Alternatively, understanding the mechanisms by which CR increases tumor latency and slows tumor progression may help to identify CR mimetics with chemopreventive properties [reviewed in (Hursting et al. 2010)].

ii. Pharmaceuticals

a. Type II diabetes and metformin—Type II diabetes currently affects approximately 15% of the adult population in the US, and the prevalence of this obesity-associated co-morbidity is on the increase (Boyle, et al. 2010). Epidemiologic data support an association between diabetes and increased risk of certain cancer types, including breast cancer (De Bruijn, et al. 2013; Giovannucci, et al. 2010; Larsson, et al. 2007; Tsilidis, et al. 2015b). Although not all studies have reported subtype-specific differences in this association (Campos-Gomez, et al. 2014), there is some evidence that the association between diabetes and breast cancer risk may be stronger in postmenopausal women (Larsson et al. 2007; Michels, et al. 2003) and for hormone receptor-positive breast cancer (Michels et al. 2003). In addition, a meta-analysis of clinical trials and prospective cohort studies reported that diabetes is associated with increased breast cancer-specific mortality, although subtype was not examined (De Bruijn et al. 2013). In direct contrast to the positive association with breast cancer risk, there is an inverse association between diabetes and total prostate cancer incidence (Kasper and Giovannucci 2006; Zhang, et al. 2012). Temporal analysis has

demonstrated that longer duration of diabetes is more protective for total prostate cancer risk (Kasper, et al. 2009; Tsilidis, et al. 2015a), suggesting that the metabolic and hormonal environment of advanced/end stage diabetes, characterized by reduced bioavailable testosterone and low insulin, is consistent with protection from total prostate cancer incidence (Allott, et al. 2013a; Kasper and Giovannucci 2006). However, longer duration of diabetes in obese men was associated with increased risk of metastasis following radical prostatectomy (Wu, et al. 2013), and diabetes has been associated with increased risk of prostate cancer-specific mortality (Cai, et al. 2014), suggesting that the low insulin environment of advanced diabetes may select for more aggressive prostate cancers which can survive in this environment (Allott et al. 2013a). Therefore, while associations with diabetes are contrasting for breast and prostate cancer incidence, associations with cancer progression and mortality are consistent for both tumor types.

Relative to other anti-diabetic therapies, metformin has been associated with reduced total cancer incidence in some (Decensi, et al. 2010; Evans, et al. 2005), but not all studies (Tsilidis, et al. 2014), and with decreased cancer-specific mortality (Currie, et al. 2012, Lega, et al 2014). In line with these findings, evidence supporting a role for metformin in breast cancer is somewhat mixed. A meta-analysis reported that metformin use was associated with reduced breast cancer incidence and mortality (Zhang, et al. 2013), but other studies failed to demonstrate a protective effect of metformin on breast cancer incidence (Franciosi, et al. 2013; Kowall, et al. 2015; Tsilidis, et al. 2014) or mortality (Lega, et al. 2014). Furthermore, there is inconsistent evidence for differences in these associations by breast cancer subtype, with one study reporting a larger proportion of progesterone receptor-positive tumors in metformin users versus non-users (Berstein, et al. 2011), while another study did not find any difference in the frequency of hormone receptor-positive tumors by metformin use (Besic, et al. 2014). A trial in which women were randomized to metformin one month prior to breast cancer surgery found that metformin use reduced Ki67 expression in HER2-positive resected tumors (DeCensi, et al. 2014), while another study reported that metformin use was associated with reduced HER2-positive breast cancer-specific mortality (He, et al. 2012). In support of these epidemiologic data, preclinical data show that metformin suppressed overexpression of the HER2 protein via Akt/mTOR pathway inhibition (Vazquez-Martin, et al. 2009), and delayed the onset of adenocarcinoma in a transgenic mouse model of HER2-positive breast cancer (Anisimov, et al. 2010). However, metformin has also been shown to slow tumor growth in an ER-positive mouse model of breast cancer, via suppression of obesity-associated adipokine levels and reduced Akt/mTOR pathway activation (Fuentes-Mattei, et al. 2014), suggesting that the potential chemopreventive effect of metformin may not be limited to HER2-positive tumors. Finally, a preclinical study reported that metformin does not impact tumor growth in nondiabetic rat and mouse models (Thompson, et al. 2015), a finding supported by epidemiologic data that metformin impacts Ki67 tumor expression in insulin resistant but not in insulin sensitive women (DeCensi et al. 2014).

In prostate cancer, although some studies report inconsistent findings (Azoulay, et al. 2011; Currie, et al. 2009; Franciosi, et al. 2013; Murtola, et al. 2008; Wright and Stanford 2009), mounting evidence supports an inverse association between metformin use and prostate cancer risk in men with diabetes (Clyne 2014; Preston, et al. 2014; Yu, et al. 2014a). Fewer

studies have examined the association between metformin use and prostate cancer recurrence and mortality, with somewhat mixed results. While several individual studies reported null findings (Allott et al. 2013a; Kaushik, et al. 2013; Patel, et al. 2010), a meta-analysis demonstrated that metformin use was associated with reduced risk of recurrence following primary therapy (Yu et al. 2014a), and there is evidence to support an inverse association between metformin use and prostate cancer-specific mortality (Bensimon, et al. 2014; Margel, et al. 2013), although this has not been reported by all studies (Lega, et al. 2014). Further supporting a chemopreventive role for metformin in prostate cancer, metformin slowed tumor growth in a xenograft mouse model of prostate cancer (Ben Sahra, et al. 2008), in addition to reducing IGF1 levels and modestly counteracting the tumor-promoting properties of a high fat diet in a small study using the TRAMP model (Xu, et al. 2014). Finally, metformin reduced mouse prostatic intraepithelial neoplasia (mPIN) development and slowed transition to adenocarcinoma in the Hi-Myc transgenic mouse model of prostate cancer, via down regulation of Myc gene expression (Akinyeke, et al. 2013).

While data from both preclinical and population-based studies support an antineoplastic role for metformin, translating findings from laboratory studies to humans is rendered more challenging by high metformin doses commonly used in animal and cell-based models, often exceeding recommended therapeutic doses in humans (Ben Sahra, et al. 2010). In addition, the progressive nature of diabetes and the various medications used to control it makes population-based research into the impact of metformin on cancer risk and mortality somewhat challenging. Time-related biases are a consideration in observational studies of drug use and may lead to overestimation of the inverse association between metformin and cancer (Suissa and Azoulay 2012). However, a meta-analysis of prospective studies which controlled for obesity status and which were not subject to time-related biases concluded that metformin was associated with a modest reduction in overall cancer risk (Gandini, et al. 2014). Whether metformin should be considered as a chemopreventive agent for individuals without diabetes is another issue. Preclinical studies have demonstrated direct action of metformin on cancer cells through AMPK activation and mTOR signaling (Hardie and Alessi 2013; Zhou, et al. 2001), suggesting that metformin may also have chemopreventive properties in individuals without insulin resistance or diabetes. However, a body of evidence in both population and preclinical mouse models suggests that metformin impacts tumor growth only in the context of insulin resistance, obesity, and/or diabetes, indicating that improving insulin sensitivity may be a key indirect mechanism by which metformin impacts cancer growth (Bonanni at al. 2012; DeCensi et al. 2014; Thompson et al. 2015). This proposed mechanism is further supported by evidence linking elevated levels of C-peptide (a surrogate for insulin levels) with breast and prostate cancer-specific mortality (Goodwin, et al. 2012; Ma, et al. 2008). Therefore, while evidence suggests that metformin may be most beneficial for preventing cancer growth in insulin resistant individuals via indirect mechanisms, future studies should explore potential direct mechanisms using preclinical models and metformin doses which reflect those used in humans.

b. Inflammation and non-steroidal anti-inflammatory drugs—Chronic, low-grade inflammation is a hallmark of obesity, and has been proposed as a mechanistic link between

obesity and cancer (Colotta, et al. 2009). Metabolism of arachidonic acid, a major component of animal fat, by cyclooxygenase (COX) generates prostaglandin and other eicosanoids, a group of biologically active lipids that play a key role in inflammation. Obesity is associated with elevated levels of COX-2 expression and heightened prostaglandin signaling (Subbaramaiah, et al. 2012), suggesting a targetable inflammatory mechanism linking obesity and cancer. The anti-inflammatory properties of non-steroidal anti-inflammatory drugs (NSAIDs) are mediated via COX inhibition which, in turn, reduces prostaglandin levels (Wang and Dubois 2010). While the strongest evidence for a role for NSAIDs in chemoprevention comes from inverse associations with adenoma and colorectal cancer (Baron, et al. 2003; Rostom, et al. 2007), there is also support for a role for NSAIDs in other cancer types (Wang and Dubois 2010).

While normal breast tissue expresses low levels of COX-2, approximately 40% of invasive breast cancers overexpress this enzyme, and elevated levels are associated with increased risk of breast cancer-specific mortality (Ristimaki, et al. 2002). The inverse association between NSAID use and breast cancer incidence does not appear to differ significantly by drug type, with similar effect estimates reported for both aspirin and non-aspirin NSAIDs (de Pedro, et al. 2015). However, a randomized trial of low-dose aspirin failed to demonstrate an inverse association for breast cancer incidence (Cook, et al. 2005), potentially suggesting that a higher dose may be required for chemoprevention. Some studies report that the protective association between NSAID use and breast cancer is limited to hormone receptor-positive disease (de Pedro et al. 2015; Terry, et al. 2004), and others have reported a stronger inverse association between NSAID use and breast cancer-specific mortality in hormone receptor-positive cases (Allott, et al. 2014d). Given that COX-2-mediated prostaglandin production promotes estrogen biosynthesis via up regulation of the aromatase pathway (Zhao, et al. 1996), there is biologic rationale to support a role for NSAIDs in suppressing hormone receptor-positive breast cancer incidence and progression. Indeed, NSAID use is associated with reduced serum estradiol levels in women with breast cancer (Hudson, et al. 2008), which may impact the growth of estrogen-responsive tumors. Finally, in further support of a true biologic association between NSAID use and breast cancer, there is evidence that longer duration of NSAID use is more protective for both breast cancer incidence (Terry et al. 2004) and breast cancer-specific mortality (Allott et al. 2014d).

Studies in breast cancer mouse models support a role for COX-2 in promoting tumor growth (Liu, et al. 2001; Lyons, et al. 2011) and for selective COX-2 inhibitors, including celecoxib, in inhibiting tumor growth (Chang, et al. 2004). One study showed that celecoxib was most protective in HER2-expressing mouse models of breast cancer, via reduction of prostaglandin levels (Howe, et al. 2002), indicating a potential role for COX-2 inhibition in preventing HER2-positive breast cancer. However, while COX-2 overexpression has been reported in HER2-positive breast cancers in women (Ristimaki et al. 2002; Subbaramaiah, et al. 2002), the impact of NSAID use in this tumor subtype has not been widely examined, perhaps due to the relatively low frequency of HER2-enriched breast cancers in the human population. Finally, a study in a rat model of breast cancer showed that NSAIDs were only effective in hormone-responsive tumors (Woditschka, et al. 2008), supporting epidemiologic

literature reporting stronger associations between NSAID use and hormone receptor-positive breast cancer risk and mortality.

Similar to breast cancer, there is evidence for overexpression of COX-2 in prostate cancer, relative to non-cancerous tissue or benign prostatic hyperplasia (Yoshimura, et al. 2000), and elevated expression is associated with increased prostate cancer-specific mortality (Khor, et al. 2007). A meta-analysis reported an inverse association between NSAID use and aggressive prostate cancer risk which was strongest amongst aspirin users, particularly longer duration aspirin users (Liu, et al. 2014). However, a randomized trial of celecoxib for 4-6 weeks in patients with localized prostate cancer had no impact on prostaglandin levels in the prostate (Antonarakis, et al. 2009), potentially suggesting an exposure period of insufficient length to impact prostate cancer biology. Interestingly, the association between aspirin use and aggressive prostate cancer incidence appears to differ by geographic region, with a significant protective effect evident in North American, but not in European studies (Liu et al. 2014; Wang, et al. 2014). Given that anti-inflammatory agents such as NSAIDs can lower PSA levels (Chang, et al. 2010), this geographic disparity in results may be attributable in part to differences in screening practices. However, one North American study where prostate cancer screening was largely independent of PSA testing reported that aspirin and NSAID use was associated with reduced risk of aggressive disease (Vidal, et al. 2014), supporting a true biologic association between NSAID use and prostate cancer. Finally, a number of studies in the TRAMP mouse model of prostate cancer support a role for COX inhibition in prostate cancer chemoprevention, reporting that celecoxib reduced tumor size (Gupta, et al. 2004), caused regression of mPIN lesions (Narayanan, et al. 2004) and inhibited the development of adenocarcinoma in a dose-dependent fashion (Narayanan, et al. 2006).

One limitation of many observational studies of NSAID use is incomplete capture of NSAID use information, with many studies focusing solely on aspirin or ibuprofen use, or on prescription NSAIDs only (Allott et al. 2014d; de Pedro et al. 2015). Incomplete NSAID use data may attenuate the association between NSAID use and cancer, since "unexposed" individuals may have taken other types of NSAIDs that were not ascertained during data collection, especially given the widespread use of these drugs. In addition, confounding by indication is an important consideration in observational studies of NSAID use, as users may be more likely to have chronic conditions such as arthritis for which they are taking NSAIDs (Allott et al. 2014d). Finally, although epidemiologic and preclinical evidence supports a role for COX inhibition in chemoprevention, the clinical utility of selective COX-2 inhibitors is limited due to cardiovascular and gastrointestinal side effects (Wang and Dubois 2010). As such, understanding the mechanisms linking NSAID use and cancer will result in the identification of additional biomarkers and therapeutic targets, potentially enabling the development of therapeutic agents with fewer side effects than existing COX inhibitors.

c. Hypercholesterolemia and statins—Hypercholesterolemia, an obesity-associated co-morbidity, affects approximately 20% of the US adult population (Fryar, et al. 2012). Cholesterol is an essential plasma membrane component of animal cells and plays a crucial role in maintaining membrane fluidity, in addition to regulating intracellular signaling

processes (Krycer and Brown 2013). The role of cholesterol as the precursor for endogenous sex steroid biosynthesis suggests its potential importance in both breast and prostate cancer, two hormone-dependent tumor types.

Dietary cholesterol intake is associated with increased risk of breast cancer, with evidence for a dose-dependent effect across increasing quartiles of cholesterol intake (Hu, et al. 2012). Moreover, a large prospective study of over one million adults in Korea showed that serum cholesterol levels were associated with increased risk of breast cancer (Kitahara, et al. 2011). Consistent with the role of cholesterol as a precursor for sex steroid biosynthesis, studies which stratified by hormone receptor status reported that elevated serum cholesterol levels were associated with increased risk of hormone receptor-positive disease (Fagherazzi, et al. 2010) and that high dietary cholesterol intake was associated with increased risk of ER-positive, but not ER-negative disease (Jakovljevic, et al. 2002). Finally, a recent study demonstrated that 27-hydroxycholesterol (27-HC), the most abundant cholesterol metabolite in the circulation and an endogenous selective estrogen receptor modulator (SERM), promoted ER-positive breast cancer progression in multiple mouse models (Nelson, et al. 2013), suggesting a mechanistic link between cholesterol and breast cancer.

Relative to other organs of the body, normal prostate epithelial cells have high cholesterol content and these levels increase further during progression to prostate cancer (Krycer and Brown 2013), suggesting that cholesterol accumulation may be advantageous to prostate cancer progression. In support of this hypothesis, hypermethylation of the cholesterol efflux transporter ABCA1, an epigenetic silencing mechanism leading to accumulation of intratumoral cholesterol, has been associated with increased risk of aggressive prostate cancer (Lee, et al. 2013). There is a suggestion that elevated cholesterol may be associated with increased risk of aggressive prostate cancer (Farwell, et al. 2011; Mondul, et al. 2011; Platz, et al. 2008; Platz, et al. 2009; Shafique, et al. 2012) but not total prostate cancer (Mondul, et al. 2010; Platz et al. 2008), although other studies have reported no association between cholesterol or its sub-fractions and prostate cancer risk (Jacobs, et al. 2012; Martin, et al. 2009). While studies examining prostate cancer progression are few, positive associations between elevated serum cholesterol levels and risk of prostate cancer recurrence (Allott, et al. 2014b) and mortality (Batty, et al. 2011) have been reported. In support of these epidemiologic associations, cholesterol has been shown to promote prostate cancer cell line growth *in vitro* and *in vivo* (Zhuang, et al. 2002), while reduction of serum cholesterol levels lowered intratumoral androgen levels and slowed tumor growth in xenograft mouse models of human prostate cancer (Mostaghel, et al. 2012), supporting the hypothesis that steroid biosynthesis may be an important mechanism linking cholesterol and prostate cancer.

Statins are cost-effective and widely prescribed cholesterol-lowering drugs with proven benefits for cardiovascular disease prevention (Ridker and Cook 2013), and are used by approximately one in every four adults in the US population (Gu Q 2014). Statin use has been associated with reduced total cancer risk (Farwell, et al. 2008) and lower cancer-specific mortality (Nielsen, et al. 2012) via a number of potential mechanisms including mevalonate pathway inhibition (Pelton, et al. 2012), reduced inflammation and angiogenesis (Pelton et al. 2012) and lower serum cholesterol levels (Demierre, et al. 2005). Given that

the bioavailability of statins in the circulation is low (Roy, et al. 2011), their cholesterol-lowering properties may be the most relevant for breast and prostate cancers.

Despite biologic rationale for a role of statins in breast cancer chemoprevention, the majority of evidence supports no association between statin use and total breast cancer risk (Bonovas, et al. 2005; Undela, et al. 2012), and studies examining this association by breast cancer subtype are few. While one study reported reduced rates of ER-negative breast cancers among statin users (Kumar, et al. 2008), another found a null association overall and no evidence of effect modification by hormone receptor status (Desai, et al. 2013). However, epidemiologic evidence supports an inverse association between statin use and risk of breast cancer recurrence and mortality. Statin use after a breast cancer diagnosis has been associated with reduced risk of recurrence, with a stronger association for lipophilic statins (Ahern, et al. 2011; Kwan, et al. 2008). Furthermore, a study of over 30,000 breast cancer cases in the Finnish Cancer Registry showed an inverse effect of both pre and post-diagnosis statin use on breast cancer-specific mortality, with evidence for a dose and time-dependent effect among pre-diagnosis users (Murtola, et al. 2014). Another study in the UK Cancer Registry also reported a weak protective effect of statin use on breast cancer-specific mortality, with some evidence that simvastatin use showed the strongest association (Cardwell, et al. 2015). Studies stratifying by hormone receptor status are required, as this information has been lacking in previous studies (Cardwell et al. 2015; Murtola et al. 2014).

In prostate cancer, while the preponderance of evidence does not support an association between statin use and total prostate cancer risk (Bansal, et al. 2012; Bonovas, et al. 2008; Browning and Martin 2007; Dale, et al. 2006; Kuoppala, et al. 2008), an inverse association between statin use and risk of aggressive disease has been consistently reported (Bansal et al. 2012; Bonovas et al. 2008). Regarding prostate cancer outcomes after treatment, three meta-analyses have reported a null association between statin use and risk of recurrence (Mass, et al. 2012; Park, et al. 2013; Scosyrev, et al. 2013). However, the studies contributing to these meta-analyses were few and most examined statin use at the time of prostate cancer treatment. Given the widespread use of statins, it is likely that many nonusers became statin users after treatment, which may bias the results of these previous studies towards the null. A retrospective analysis which minimized misclassification of statin users by excluding prevalent users at the time of prostate cancer treatment and capturing statin use throughout the follow up period showed that post-diagnosis statin use was associated with reduced risk of recurrence (Allott, et al. 2014a), suggesting a true protective association between statin use and prostate cancer. Finally, an analysis of almost 12,000 men with localized prostate cancer showed that post-diagnostic statin use was associated with reduced prostate cancer-specific mortality, with evidence for a stronger protective effect amongst those who had also used statins before diagnosis (Yu, et al. 2014b). Given that cardiovascular disease and cancer are the two most common causes of mortality in the US (American Society of Clinical 2014), understanding the potential role of cholesterol reduction for cancer prevention will have important public health impact.

5. Transdisciplinary challenges facing obesity and cancer research

Obesity is a complex and heterogeneous exposure, giving rise to a number of considerations and challenges for obesity and cancer research, particularly in translating findings from preclinical to population-based research, and *vice versa*.

First, inter-individual variation in adipose tissue distribution leads to challenges in defining obesity status for population-based research. BMI is a well-validated surrogate of overall obesity with the important strength of being widely used, thus enabling inter-study comparisons (Allott et al. 2013b). However, visceral obesity, accumulation of adipose tissue within the abdominal cavity, is a risk factor for cardiovascular disease (Neeland, et al. 2013) and certain types of cancer, including breast and prostate (Doyle, et al. 2012; Pischon, et al. 2008). Population-based studies rely on waist circumference and waist-to-hip ratio as surrogates of visceral obesity, given that computed tomography (CT), the gold standard method for direct quantification of visceral fat area (VFA), is not feasible for population-based research. While these surrogate measures correlate more strongly with VFA than BMI does (Allott, et al. 2014c), it is important to consider that they do not distinguish between subcutaneous and visceral adipose tissue at waist level (Figure 4), potentially giving rise to some misclassification of visceral obesity status. Despite this limitation, waist circumference and waist-to-hip ratio offer advantages over BMI for estimating visceral obesity, given that these measures are less influenced by lean body mass. Of note, the prevalence of visceral obesity (measured by VFA or waist circumference) in the US population is higher than that of overall obesity (measured by BMI), with approximately 45% of men and women classified as viscerally obese by VFA (Pou, et al. 2009), and approximately 40% of men and 60% of women classified as viscerally obese by waist circumference (Li, et al. 2007), while only one third of individuals are classified as obese by BMI (Ogden, et al. 2014). As such, defining obesity using BMI underestimates the prevalence of visceral obesity in the population. Moreover, roughly 20% of men and 10% of women with BMI ≥ 30 kg/m^2 do not have elevated VFA, while approximately 10% of men and women with BMI <30 kg/m^2 have elevated VFA (Pou et al. 2009). Misclassification of visceral obesity status contaminates the "unexposed" (i.e. non-obese) group with "exposed" individuals (i.e. viscerally obese) and *vice versa*, with the likely result of biasing associations between obesity and cancer towards the null (Figure 5).

Second, adipose tissue is a unique organ in its ability to expand and contract throughout the life course of the individual, and the relevant timing or "window of susceptibility" for obesity to impact tumor growth is unknown. Furthermore, population-based studies that examine weight change over the life course are usually limited to self-reported obesity status, and often require individuals to recollect their body weight many decades in the past. However, while self-reported weight is known to be systematically underreported, it remains predictive of obesity-associated co-morbidities and is not outperformed by corrected measures, indicating that it may be sufficient for population-based obesity and cancer research (Dutton and McLaren 2014). Another consideration is that population-based studies of weight change across the life course are limited both by relatively rare occurrences of weight loss and by unknown reasons for weight loss. As such, preclinical models provide an opportunity to evaluate the impact of diet-induced obesity and weight loss at different

"windows of susceptibility" over the life course of the mouse, for example, post pregnancy (Sundaram, et al. 2014a). Careful design of preclinical studies with a consideration for timing of weight change in relation to tumor development will help to inform research questions in the population-based setting.

Finally, obesity is a heterogeneous phenotype, and it may be useful to consider it a disease comprised of distinct subtypes (Field, et al. 2013). For example, individuals with elevated BMI may be further stratified according to visceral obesity, diabetes or metabolic syndrome status. This research approach may help us to determine, for example, whether high cholesterol or insulin resistance rather than obesity *per se* are the driving forces behind the obesity-cancer link. Large, population-based studies with sufficient power for stratified analysis by various components of obesity are required for this approach. In addition, while pharmacoepidemiologic studies provide insight into potential chemopreventive properties of a number of medications which are widely used in the treatment of obesity-associated co-morbidities, these studies are subject to confounding by indication, in addition to other biases inherent in retrospective, observational studies of drug use. As such, results from population-based studies should be interpreted alongside preclinical findings, and alongside randomized controlled clinical trials.

6. Conclusions

The obesity-cancer link is of public health interest given the pervasiveness of both conditions, and the potentially modifiable nature of obesity. Although calorie restriction and weight loss are some of the most effective approaches for inhibiting tumor growth in animal models, weight loss is challenging for humans to achieve and maintain. Furthermore, observational data supporting a role for weight loss in cancer incidence and mortality in humans are lacking, and neither have clinical trials been conducted. While some epidemiologic and preclinical data suggest a chemopreventive role for agents targeting obesity-associated comorbidities, including metformin, NSAIDs and statins, not all studies support these findings and further research is needed. Given that preclinical models may be limited by their relevance to human cancers and observational studies are limited by non-randomized design, integrating findings from different disciplines using a transdisciplinary approach may help us to gain insight into mechanisms linking obesity and cancer. An improved understanding of the mechanisms contributing to the obesity - cancer link will be important for cancer prevention and treatment efforts. In addition, given that the top five causes of mortality in the US are heart disease, stroke, diabetes, kidney disease and cancer (Schmitz et al. 2013), targeting obesity is relevant not only to improve cancer-specific outcomes but also to impact all-cause mortality among cancer survivors.

Acknowledgments

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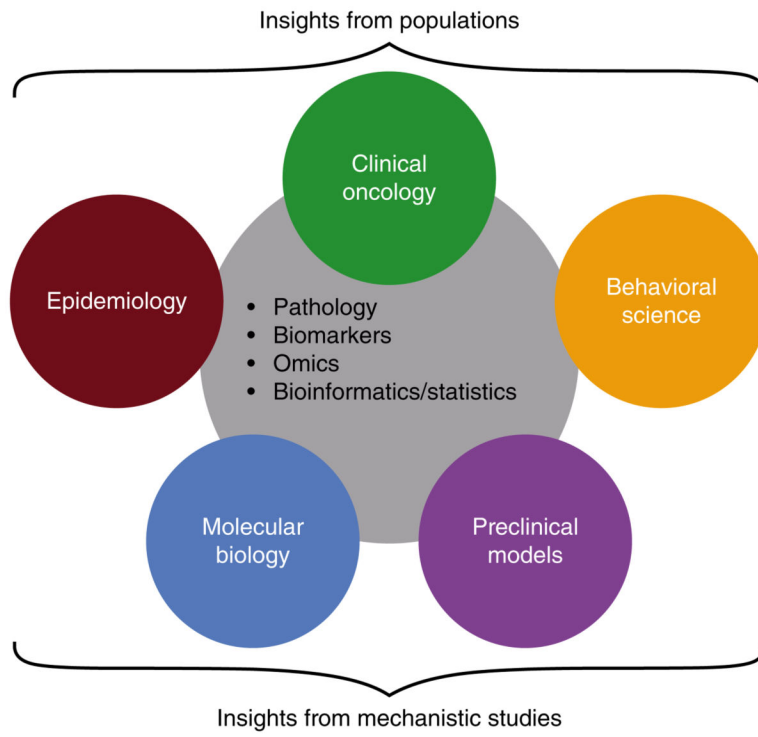
Figure 1.
Using a transdisciplinary approach to study mechanisms linking obesity and cancer.
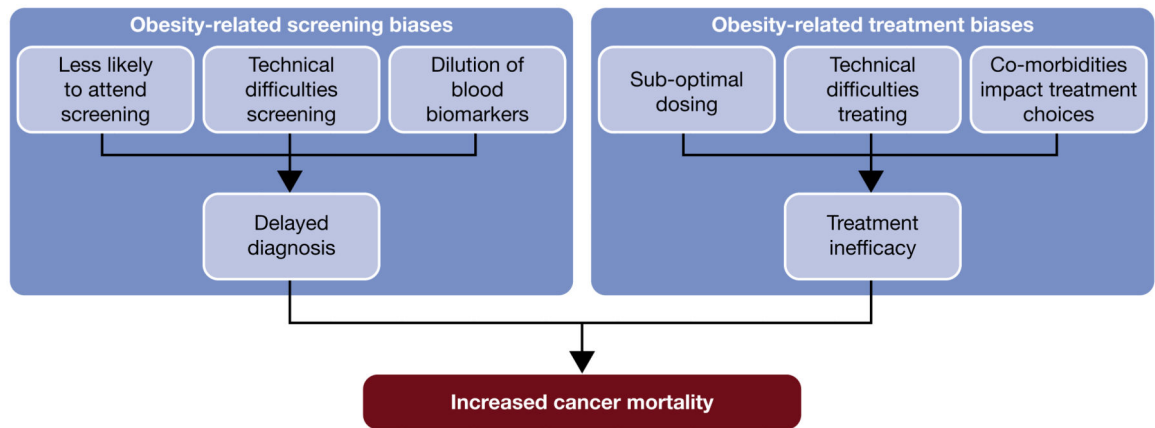
Figure 2.
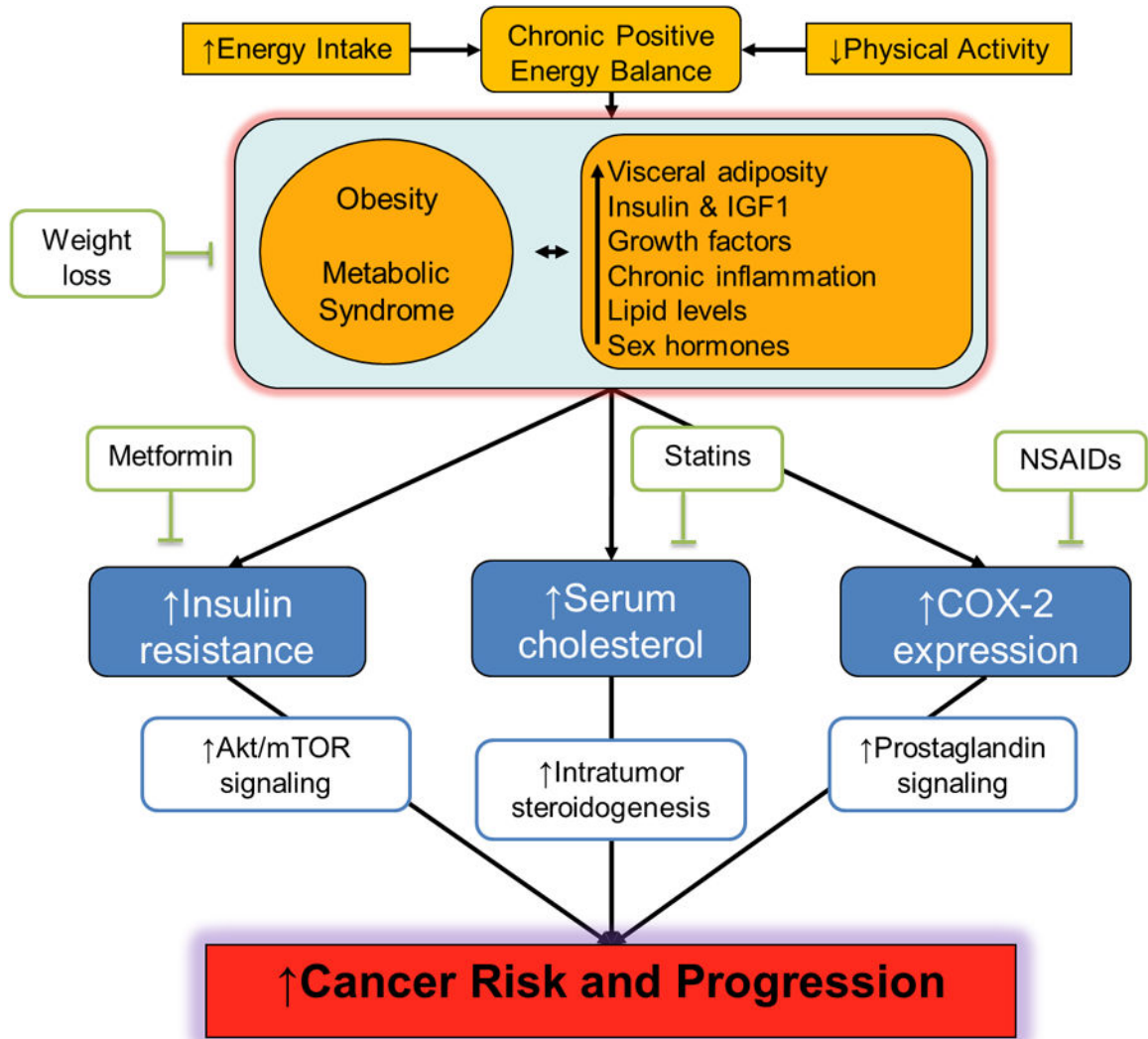Non-biologic mechanisms linking obesity and cancer mortality.

Figure 3.
Putative mechanisms linking obesity with cancer risk and progression: lessons from studies of chemopreventive agents
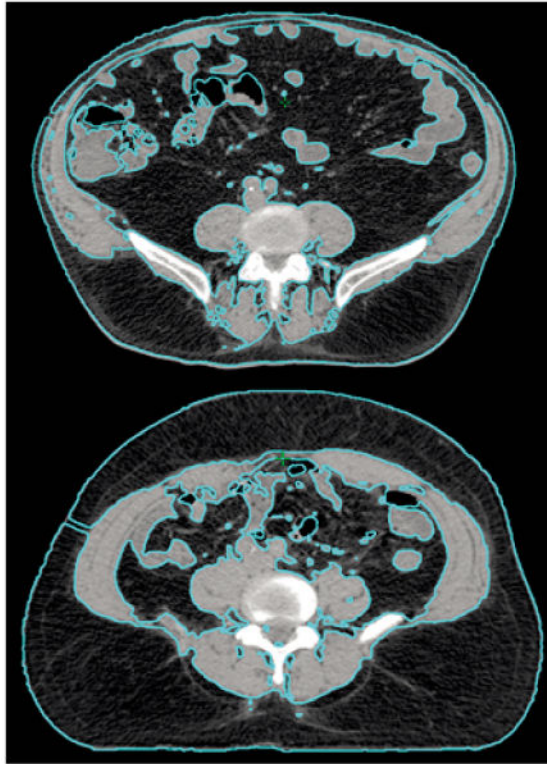
Figure 4.
Computed tomography (CT) scans of two individuals with similar waist circumference (WC) but different amounts of visceral and subcutaneous fat area, illustrating the potential for misclassification when using WC as a surrogate of visceral obesity.
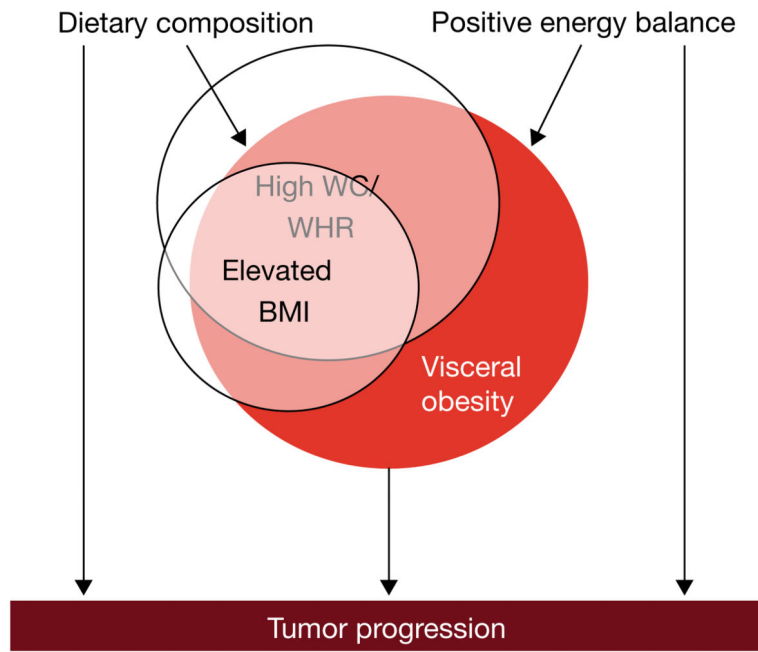
Figure 5.
Challenges associated with studying obesity: defining the exposure, and potential confounders.