

Obesity and prostate cancer: collateral damage in the battle of the bulge

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1. ABSTRACT

Prostate cancer is the most common non-cutaneous malignancy diagnosed in US men. With the increasing prevalence of obesity, it is of interest how this condition impacts prostate cancer. However, only recently has the relationship between obesity and prostate cancer been earnestly studied by investigators. Indeed, the relationship between obesity and prostate cancer appears to be complex one. Therefore, we sought to review the most recent and relevant epidemiological data discussing the link between prostate cancer and obesity. In this review, we will discuss both “biological” and “non-biological” means by which obesity may potentially impact prostate cancer.

2. INTRODUCTION

Within the last two decades, the prevalence of obesity in the United States has doubled. Currently, 30% of Americans are considered obese (Figure 1 Data from the National Health Examination survey (NHES) and National Health and Nutrition Examination Survey (NHANES).http://www.cdc.gov/nchs/products/pubs/pubd/hstats/overweight/overweight_adult.htm) (1). Though rates are highest in the US, trends for increasing obesity are being seen in central and eastern Europe (2). It has long been known obesity is associated with co-morbidities such as cardiovascular disease, diabetes, and arthritis (3). Obesity has also been linked with increased risk for several

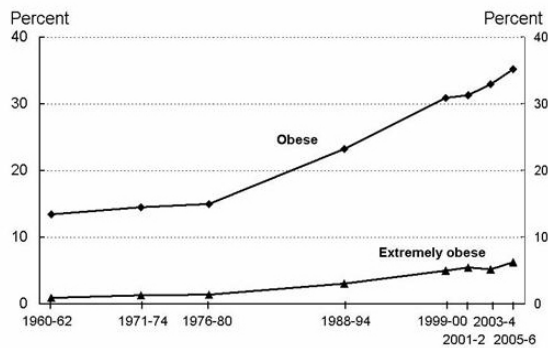


Figure 1. Trends in obesity among US adults, aged 20-74. (Data from the National Health Examination survey (NHES) and National Health and Nutrition Examination Survey (NHANES). Available at: http://www.cdc.gov/nchs/products/pubs/pubd/hestats/overweight/overweight_adult.htm. Accessed July 25, 2010.

malignancies, including prostate cancer (4, 5). Prostate cancer is the second most commonly diagnosed malignancy in men worldwide and the most common in the Western world (6). Likely the consequence of multiple factors (e.g. prostate-specific antigen (PSA) screening, access to healthcare), industrialized nations account for ~75% of known prostate cancer cases (Figure 2) (7). Over the past 20 years, the United States has seen a dramatic increased incidence of prostate cancer, accompanied by declines in mortality (7), which may in part be attributable to PSA screening (8, 9). Given the increasing prevalence of both prostate cancer and obesity, investigators have recently begun to explore the link between these two conditions.

At first glance, the data appear to offer no consensus regarding the role of obesity in prostate cancer development and progression. However, with further exploration into how obesity impacts prostate cancer incidence, progression, and mortality separately, a clearer picture of how these two disease processes interact comes into view. While it is important to understand the potential association between obesity and prostate cancer, it is equally important to clarify how obesity mediates its effects via both biological and non-biological means. Obesity is more than just excess body fat: it is associated with alterations in the systemic hormonal milieu. Indeed, obesity alters serum levels of sex steroid hormones, insulin, insulin-like growth factor-1 (IGF-1), leptin, and other hormones, all of which have been linked to prostate cancer in some studies. Beyond this, obesity is a condition whose etiology is thought to be the result of dietary excess in terms of the quantity and quality of calories consumed (e.g. dietary fat, simple carbohydrates) consumed, both of which have been linked to cancer (10). In this article, we will first review recent studies examining prostate cancer incidence, progression, and mortality and how they relate to obesity. We will then conclude with a brief overview of some of the key hypothesized mechanisms that may underscore these associations. Importantly, due to space limitations, we will not address the role of diet in mediating the link between obesity and prostate cancer, though the reader is referred to the following reviews (11, 12).

3. OBESITY AND RISK OF PROSTATE CANCER DIAGNOSIS

Obesity is defined as “a condition characterized by excessive accumulation and storage of fat in the body” (13), and results when energy intake exceeds expenditure. The World Health Organization categorizes individuals as either overweight or obese when the body mass index (BMI) is more than 25 and greater than or equal to 30 kg/m², respectively (14). A surrogate anthropometric measure of adiposity, BMI (weight in kilograms divided by height in meters squared) is strongly correlated with total body fat. BMI, while easy to determine, is not without its limitations (15). As BMI does not factor in body habitus or composition, individuals of high muscle mass and low body fat can be inaccurately reported as overweight or obese. As such, percent body fat, skin-fold thickness, and waist-to-hip ratio (WHR) have been suggested as more accurate alternative means of assessing body fat. While one study found that WHR – a measure of central adiposity – was predictive of prostate cancer risk independent of BMI (16), most studies found similarities between BMI and some the aforementioned alternatives in their ability to predict clinical outcomes (17, 18). Therefore, BMI, regardless of its limitations, stands as an acceptable measure and surrogate of obesity. Accepting of BMI’s limitations, it is the most commonly cited measurement in the literature and therefore the one primarily referred to in this review.

To date, the epidemiologic data are conflicting as to the relationship between adult obesity and prostate cancer risk. Several large cohort studies found an association between elevated risk of prostate cancer diagnosis with increasing adult BMI, though the majority of these associations were weak (19-22). In a cohort of health professionals, Giovannucci *et al.* observed not only an absence of any positive association, but found an inverse relationship between prostate cancer diagnosis and adult BMI in both the original and follow-up investigations, but only among men younger than age 60 or those who reported a family history of prostate cancer (18, 23). In contrast to the aforementioned associations, several studies found no association between adult BMI and prostate cancer diagnosis (24, 25). In attempt to come to a consensus, a meta-analysis, which examined the role of obesity in prostate cancer found a significant, but weak increased risk of cancer diagnosis (26). Since the publication of this meta-analysis, several studies – mostly from the United States – all found obese men were actually less likely to be diagnosed with prostate cancer (23, 27, 28).

Given the weak association with adult BMI and the prolonged natural history of prostate cancer, it is possible that circumstances in childhood or early adulthood may predispose to prostate cancer later in life. Viewed alternatively, by focusing on adult BMI it is possible the window of time that increased BMI and its sequelae impacted prostate cancer risk was overlooked. Several studies examined the relationship between pre-, peri-, and post-pubertal obesity and prostate cancer risk. Overall, the

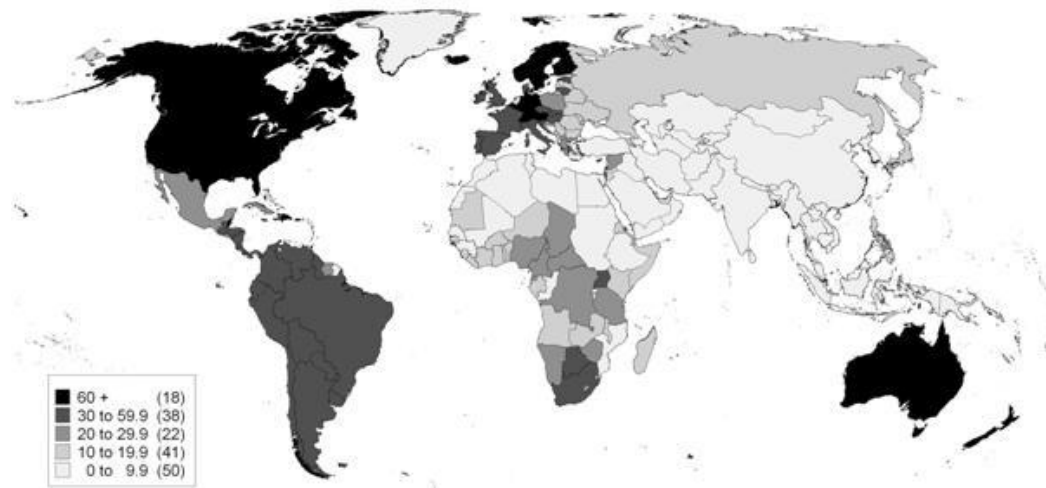


Figure 2. Global prostate cancer Incidence rates per 100000 in 2002. Data source: GLOBOCAN 2002, International Agency for Research on Cancer (IARC)). Reproduced with permission from 7.

data are conflicting, as there is evidence linking BMI within the first 3 decades of life with prostate cancer risk (22, 24), while others have shown an elevated BMI during this period affords individuals some degree of protection (29, 30). In a meta-analysis, it was concluded the relationship between BMI at these early time points and prostate cancer risk was likely a weak association (31). Notably many of the studies published were limited by the lower prevalence of obesity in childhood and young adulthood in decades past. Thus, the data concerning early life BMI and prostate cancer risk are inconclusive and beg further investigation.

Beyond examining the association between obesity and risk of diagnosis, studies have sought to understand if and how BMI relates to stage and disease grade (i.e. disease aggressiveness). The data suggest obese men are less likely to be diagnosed with low grade, indolent disease than their normal weight counterparts (32, 33). Paradoxically, in these same studies, obese men were at increased risk for high grade and advanced disease (28, 32, 33).

Overall, the data suggest a weak association between adult obesity and overall prostate cancer diagnosis though there does seem to be a relatively consistent association with reduced risk of low-grade non-aggressive disease and increased risk of more aggressive disease, especially in more recent studies. At this time, we cannot speak to what effect obesity at earlier time points plays in prostate cancer risk. Obesity is known to modulate a wide range of hormones and pro-cancer pathways linked to high-grade disease (see section 5). As such it is not difficult to imagine the relationship between increasing BMI and aggressive disease. However, the relationship between obesity and lowered incidence of low grade disease is relatively unclear. There are a host of potential biological and non-biological reasons likely to explain the above observations. One such reason may be the relative difficulty of detecting prostate cancer in obese men.

4. OBESITY AND PROSTATE CANCER DETECTION

Prostate cancer detection may be hindered by several obstacles. Specifically, obesity negatively impacts screening behavior for colorectal cancer (34). In contrast, studies suggest obese men are actually more likely than normal weight individuals to undergo PSA testing (35, 36). In the PSA-era, serum PSA levels typically dictate who is recommended to undergo prostate needle biopsy. Therefore, it is particular relevant that numerous studies found an inverse relationship between BMI and PSA (37-42). We previously hypothesized the mechanism underlying this is the larger blood volume in obese men diluting the PSA (i.e. hemodilution) (43). Recent studies support this hypothesis (44-47). As prostate biopsy are typically recommended based upon cut-off values, lower PSA levels may result in the decreased likelihood of an obese man undergoing prostate biopsy. However, this rationale would apply solely to countries where PSA screening is widespread. Thus, it is noteworthy that studies linking obesity with lowered prostate cancer risk have come predominantly from the United States (18, 23, 27, 28).

Unfortunately, simply adjusting for lower PSA values is not a panacea for prostate cancer detection difficulties in obese men. As the majority of prostate cancer is clinical stage T1c (i.e. diagnosed based solely upon elevated PSA), prostate biopsies are an attempt to survey the prostate and thus locate small foci of disease should they exist. However, detection of disease may be complicated in men with larger prostate glands and indeed, obese men appear to have larger glands (48). Previously, we had postulated that nearly 1 in 4 cancers may be undiagnosed as a result of the larger prostates among obese men (49).

In summary, the literature describes several potential factors contributing to a detection bias in under-

diagnosing obese men. This is particularly well exemplified by two studies from the same group. In the first study, the authors found obesity was inversely associated with prostate cancer risk (50). Revisiting that same study population, investigators later found that when controlling for potential obstacles to detection (e.g. prostate volume, DRE findings, and PSA) obese men were at increased prostate cancer risk (51). Fortunately, many potential obstacles regarding detection are easily overcome with the institution of clinical guidelines as they pertain to PSA screening (i.e. adjusting PSA for the level of obesity) and prostate needle biopsy (taking more needle cores in larger prostates).

5. OBESITY AND ONCOLOGICAL OUTCOMES

As we consider the relationship between obesity and prostate cancer, one important question to be answered is how obesity impacts cancer control among men with prostate cancer. Most studies examining this distant clinical endpoint have done so within cohorts primarily treated with radical prostatectomy. Some studies have shown no association between increasing BMI and biochemical recurrence, though in some instances these observations were found in European cohorts where obesity is not as profound as in the US (52-55). Regardless, most studies do show obese men are at increased risk of recurrent disease (56-63). There are a number of explanations for the higher recurrence rates in these men. The obese patient presents the surgeon with a variety of technical challenges which include but are not limited to visualization of and access to the surgical field. For example, when operating on obese men, surgeons – regardless of their level of experience – are more likely to have capsular incision (64). Capsular incision – inadvertent incision though the prostatic capsule – has been associated with increased risk of biochemical recurrence (65). Perhaps more telling are the data demonstrating increased positive margin risk in obese men in both open (53, 54) and robotic radical prostatectomy cohorts (56, 57, 66, 67).

Radiotherapy is not without its own difficulties when treating the obese. However, it appears this is not uniform across various forms of radiation (i.e. external beam radiation therapy (EBRT) and brachytherapy). Specifically, obese men have higher rates of biochemical recurrence, metastases, and prostate cancer death when treated with EBRT relative to normal weight men (54, 68-71), whereas studies examining brachytherapy – the implantation of radioactive seeds into the prostate – have demonstrated no such association (72, 73). This difference between treatments may relate in part to technical issues. In brief, the efficacy of EBRT is predicated upon the prostate and prostatic bed receiving a sufficient dosage of radiation. However, the location of the prostate in obese men varies over time to a greater degree than in normal weight men (74), possibly leading to sub-therapeutic radiation levels in obese men (74, 75). Alternatively, given that brachytherapy is delivered all at once, such daily movements of the prostate are not an issue.

Indeed, the literature suggests obesity presents the clinician with obstacles that may impact cancer control

and decrease disease-free survival rates. However, even in the absence of postoperative surrogates (e.g. positive surgical margins) of suboptimal technique, obese men remain at increased risk for biochemical recurrence (76). As such, these observations collectively suggest inherent biological differences in disease aggressiveness between normal weight and obese men.

6. OBESITY AND PROSTATE CANCER-SPECIFIC MORTALITY

Obesity, either among men without known prostate cancer or at the time of diagnosis, has been associated with increased risk for prostate cancer mortality (PCM) in multiple studies (4, 20, 28, 33, 77-79). Within the CPS I and CPS II cohorts, two prospective studies which collectively followed ~900,000 cancer-free men for 13 and 14 years, respectively, men with BMI of greater than or equal to 30 kg/m² had 21% and 27% higher risk of prostate cancer death versus normal weight men (77). The impact of elevated BMI was even greater in severely or morbidly obese individuals (BMI greater than or equal to 35 kg/m²) with 34% higher risk of PCM. Similarly, Wright *et al.* also observed in a cohort of 287,760 cancer-free men the link between increased mortality with increasing BMI despite a relatively short follow-up of 5 years (28). Within the Physician's Health Study cohort, elevated BMI – regardless of whether the diagnosis of prostate cancer was made during the pre-PSA era or the contemporary time period – was associated with increased PCM (80). More recently, Parr *et al.* found morbidly obese men in an Asian-Pacific cohort were at a 45% increased risk of PCM with a trend for an 18% increased risk of death per every 5 BMI units (81). In a separate study, men in the highest BMI category had a 40% higher PCM versus normal weight individuals within a cohort of 135,000 Swedish men, illustrating the applicability of these observations in European populations (20). Demonstrating the potential detrimental effect of obesity early in life, increased BMI during early adulthood was associated with an approximate 50% increased PCM risk in yet a further study (82).

Several of the above studies found either in the pre-PSA era (77, 80) or in countries where PSA screening is not practiced (20), higher BMI increased the risk of PCM. Thus, though the biases in accurately detecting prostate cancer in obese men discussed above are likely real and very important for contemporary management of the obese man, they alone cannot explain the link between higher BMI and prostate cancer death. Therefore, it is highly likely that BMI biologically is linked with more aggressive prostate cancer. Possible mechanisms underlying this biological link are discussed in the next section.

7. OBESITY, HORMONES, AND PROSTATE CANCER

Obesity is associated with multiple hormonal alterations that may be important in prostate cancer biology. Specifically, elevated BMI is linked to abnormalities of the sex steroid hormone axis. Via

peripheral aromatization in the adipose tissue, testosterone is converted to estradiol and thus obese individuals have elevated estradiol levels with concomitant reductions in testosterone via feedback inhibition of the pituitary-hypothalamic axis (83).

The data from epidemiological studies are inconclusive as to the role of serum androgens in prostate cancer risk. Accepting the fact that testosterone is necessary for the development and growth of normal prostate epithelium, it is logical to assume that varying levels of androgens may influence tumor growth and behavior. Paradoxically, there are data to suggest that among men with prostate cancer, low serum testosterone is associated with more aggressive pathology and shorter survival (84-86). Though these retrospective findings were supported by some prospective studies (87, 88), a recent meta-analysis found no overall association between serum testosterone and prostate cancer risk or risk of high-grade disease (89). Given this, the degree to which the lower levels of testosterone in obese men explain the increased risk of more aggressive and advanced prostate cancer phenotype is unclear. Moreover, whether the lower risk of low-grade disease results from lower testosterone levels or detection bias remains unclear.

As a consequence of Huggins and Hodges's initial observation in 1941 that prostate cancer is highly sensitive to testosterone (90), investigations of prostate cancer development and progression have been dominated by androgens. However, there is a growing body of evidence suggesting estrogens may play a role. As obese men have more estrogens than leaner men, this may have a profound impact on tumor biology. Animal studies provide the most compelling data for estrogen's involvement in prostate cancer (91, 92). Specifically, Bosland *et al.* demonstrated that estradiol combined with low-dose testosterone promotes prostate cancer development in the NBL rat strain (93). Interestingly, this hormonal milieu (plentiful estrogen and low testosterone) closely resembles the hormonal profile of obese men. Moreover, estrogens can be converted to catecholestrogens which may have genotoxic properties, impairing essential DNA repair mechanisms (94, 95). Polymorphisms of estrogen-related genes have been linked to increased risk of prostate cancer diagnosis and tumor aggressiveness (96, 97). Furthermore, there are data suggesting increased expression of estrogen receptors, specifically estrogen receptor alpha, may correlate with more aggressive and advanced prostate cancer (e.g. metastatic and hormone-refractory disease) (98). Indeed, both preclinical and early stage clinical investigations using selective estrogen receptor modulators (e.g. raloxifene, toremifene), have found success in reducing the incidence of prostate cancer as well as its progression (99-103). Therefore, it appears estrogens may play some play in prostate cancer biology and that their elevated presence in obese men may contribute to poorer outcomes.

In addition, obesity significantly influences the insulin axis resulting in impaired insulin sensitivity and

hyperinsulinemia (104). Elevated insulin levels have been positively associated with prostate cancer risk, high-grade disease, and worse outcomes in some studies (105-107). In support of insulin's role in prostate cancer biology, men with increased C-peptide plasma concentrations, a surrogate marker of endogenous insulin secretion, have been found to be at elevated risk of cancer diagnosis and high-grade disease as well as PCM (80, 108). In contrast to the hyperinsulinemic state of obesity, men with diabetes, which is typically an insulin-deficient state, appear to be at decreased prostate cancer risk with a meta-analysis finding diabetes associated with an ~10% risk reduction (109).

Beyond its function as an energy storage site, adipose tissue serves as an endocrine organ. Adipocytes produce adipokines such as leptin and adiponectin. Leptin controls bodyweight by regulating energy intake and expenditure and is positively correlated with BMI (110). Though the data are inconclusive, leptin levels appear to be positively associated with not only prostate cancer risk but disease progression in some studies (111, 112), though other studies failed to find an association between leptin levels and prostate cancer aggressiveness (113, 114). Furthermore, allelic variants of the leptin gene have been associated with increased prostate cancer risk (115). Supporting these epidemiological observations, prostate cancer cell growth is augmented in the presence of leptin, though only in androgen-independent cell lines (116-118). In contrast to leptin, adiponectin, which is inversely linked with BMI (119), has been shown to be anti-cancer in its properties (120). Importantly, there are data suggesting that adiponectin levels are negatively correlated with risk of aggressive disease and PCM (114, 121, 122).

8. CONCLUSION

Given the expanding waistlines of men in industrialized nations, it is of great importance that we gain a better understanding of how obesity influences prostate cancer biology and its associated clinical outcomes. The data suggest that obese men are at increased risk for high-grade, advanced disease despite a decreased incidence of low grade, indolent disease (Figure 3). This may be explained by such obstacles to detection as falsely lowered PSA secondary to hemodilution or insufficient prostate biopsy due to enlarged prostates. Alternatively, aberrations of key hormonal axes possibly related to prostate cancer may also prove to be the cause of this observation. When obese men are diagnosed with prostate cancer, they appear to fare worse than the normal weight counterparts with respect to oncological outcomes and prostate cancer mortality, likely due to both technical difficulties resulting in sub-optimal therapy and inherently more aggressive disease (Figure 4). Though there is a growing body of evidence in support of a role for obesity in prostate cancer, the exact mechanisms through which obesity influences prostate cancer biology remains unclear and further studies are required to better understand this link. However until that time, we may be

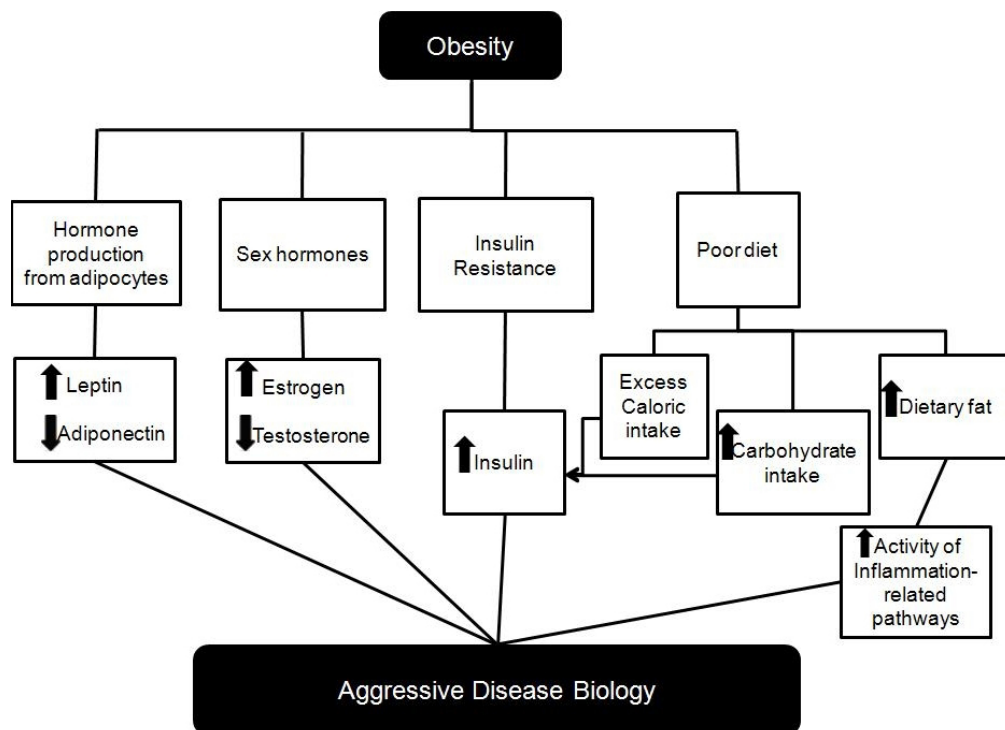


Figure 3. Obesity and aggressive prostate cancer biology.

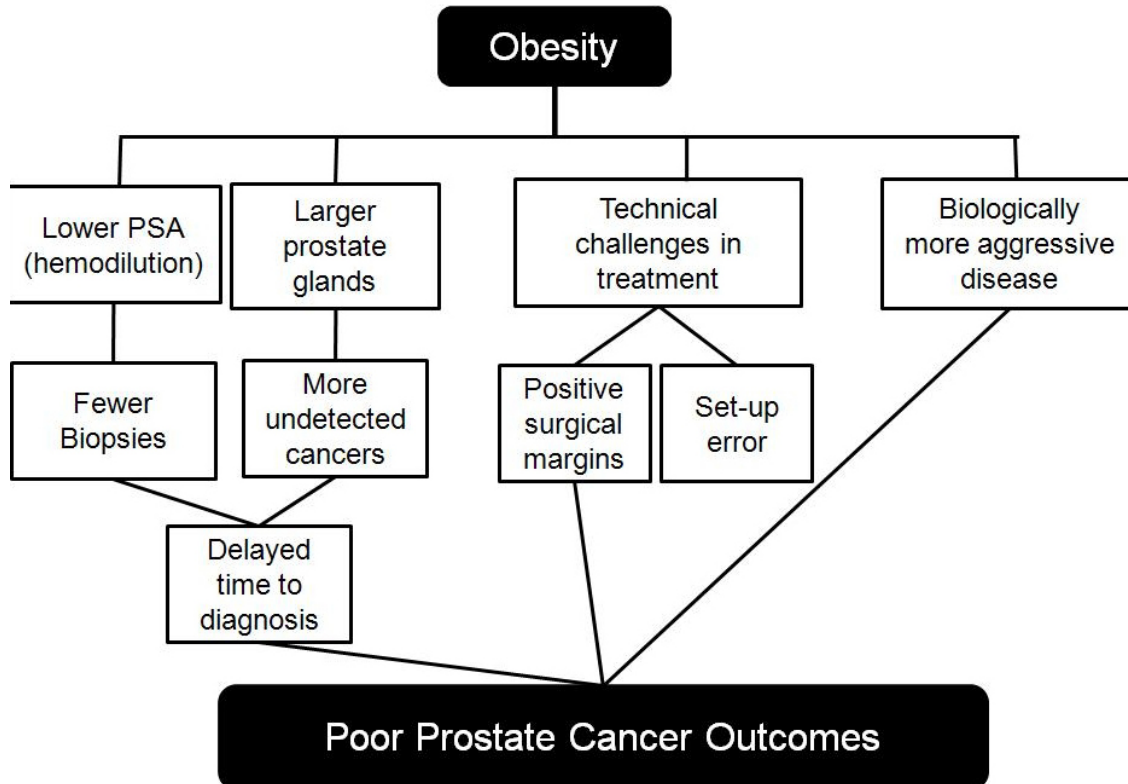


Figure 4. Obesity and poor prostate cancer outcomes.

better served by advising all men to make healthy lifestyle choices with the goal of maintaining a healthy body weight to avoid obesity. Hopefully, by counseling patients and incorporating healthy weight management protocols into the prostate cancer treatment paradigm, we can affect a significant reduction in both the incidence of prostate cancer and its mortality.

9. ACKNOWLEDGEMENTS

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