Obesity and Prostate Cancer: Making Sense out of Apparently Conflicting Data

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Both obesity and prostate cancer are epidemic in Western society. Although initial epidemiologic data appeared conflicting, recent studies, especially large prospective studies published in the past 6–12 months, have clarified the association between obesity and prostate cancer. The aim of this paper is to review the epidemiologic data linking obesity and prostate cancer, with an emphasis on new data published since 2005. A PubMed search was done on the keywords, “prostate cancer” and “obesity.” Relevant articles and their references were reviewed for data on the association between obesity and prostate cancer. Recent data suggest that obesity is associated with reduced risk of nonaggressive disease but increased risk of aggressive disease. This may in part be explained by an inherent bias in our ability to detect prostate cancer in obese men (lower prostate-specific antigen values and larger sized prostates making biopsy less accurate for finding an existing cancer). Ultimately, this leads to increased risk of cancer recurrence after primary therapy and increased risk of prostate cancer mortality. The biologic causes of these associations are likely multifactorial, although the lower testosterone levels among obese men appear to be one of the most promising explanations. The association between obesity and prostate cancer is complex. Emerging data suggest a differential effect of obesity by disease aggressiveness: obesity may reduce the risk of nonaggressive disease while it may promote aggressive disease.

body mass index; obesity; prostate-specific antigen; prostatic neoplasms; testosterone

Abbreviations: CI, confidence interval; CPS, Cancer Prevention Study; IGF-1, insulin-like growth factor 1; PSA, prostate-specific antigen; RR, relative risk.

INTRODUCTION

Obesity is a rapidly growing epidemic. Relative to 20 years ago, the prevalence of obesity among adults in the United States has doubled to 30 percent (1). Obesity is associated with numerous chronic diseases including coronary artery disease, hypertension, diabetes, asthma, and arthritis (2). Obesity has also been linked to the development of several types of cancer including postmenopausal breast cancer and colon cancer (3).

Prostate cancer is also a major public health concern. It is the most commonly diagnosed nonskin cancer and the second leading cause of cancer death among men in the United States (4). Despite the high prevalence of both prostate cancer and obesity, only recently have researchers begun to study the association between these two diseases in earnest. A PubMed literature search using the keywords, “obesity” and “prostate cancer,” in February 2007 demonstrated 243 papers, of which 180 (74 percent) were published since January 1, 2001. Thus, nearly three quarters of the world’s
literature on obesity and prostate cancer have been written in the last 6 years.

When one begins to examine the literature regarding obesity and prostate cancer, there are sufficient articles to suggest that obesity promotes, protects, or has no effect on prostate cancer. Thus, given this mixed picture in the literature, it is tempting to conclude that no association exists between obesity and prostate cancer. However, when one separates this literature into incidence, progression, and mortality, a clearer picture begins to emerge. Given the nature of prostate cancer, it is necessary to separate the literature into these groups for several reasons. First, in some cancers (i.e., pancreatic), incidence is nearly synonymous with mortality in that nearly every person diagnosed will succumb to the cancer. This is in sharp contrast to prostate cancer, where only approximately 15 percent of men diagnosed with prostate cancer will die of their disease (4). This creates a pool of less aggressive prostate cancers, often termed indolent, and a pool of more aggressive, potentially fatal cancers. Second, the prevalence of subclinical cancer for some cancers is likely very low. Again, this is in contrast to prostate cancer, where the prevalence of autopsy prostate cancer far exceeds the prevalence of clinically diagnosed prostate cancer (5). Thus, the pool of indolent cancers far exceeds the rate of clinically detected cancers. As such, any factor that affects the likelihood that someone will undergo prostate cancer screening can have dramatic effects on the observed incidence of disease. Moreover, given that prostate cancer is detected through prostate-specific antigen (PSA) screening, rectal examination, and ultimately prostate needle biopsy, any factor that affects the sensitivity or specificity of these tests can likewise affect the observed prostate cancer incidence. Recent data suggest that obesity may influence all three of these factors with potentially profound implications for interpreting the epidemiologic literature regarding obesity and prostate cancer incidence. Third, the prevalence of prostate cancer screening is unequal globally, leading to differing prostate cancer rates among different populations. Thus, in some geographic locations, most men when diagnosed have symptomatic, advanced prostate cancer compared with men in the United States, where most men when diagnosed have early stage asymptomatic, screen-detected cancers. Finally, given this pool of both aggressive and nonaggressive cancers, recent studies have suggested that some factors (i.e., testosterone and detection bias) may differentially influence the development of these cancers. Indeed, obesity may be one of these factors, as discussed below. Alternative explanations for disparate results in the literature include different measures of adiposity, differing time points at which adiposity was measured, study design differences, differences in study populations (particularly the prevalence of aggressive disease in the population being studied), and differences in the distribution of obesity (6).

It should be noted that obesity is associated with marked alterations in the serum concentrations of numerous hormones including testosterone, estrogen, insulin, insulin-like growth factor 1 (IGF-1), and leptin—all of which have been linked to prostate cancer in some studies. In addition, obesity is highly correlated with dietary intake: On average, obese men have a positive energy balance and consume greater amounts of dietary fat, both of which have been linked to cancer (7). Finally, obesity is also associated with greater production of inflammatory mediators, and inflammation has been suggested to be involved in prostate cancer development (8). As such, a comprehensive review of all the various sequelae of obesity and their possible relations to prostate cancer is beyond the scope of this review. Therefore, we will concentrate on recent studies examining the epidemiologic data relating obesity itself (predominantly increased body mass index) to risk of development, progression following therapy, and death from prostate cancer. We will highlight new data suggesting that it may be harder to detect prostate cancers among obese men, leading to delayed diagnosis. In addition, given that several reviews have been published on obesity and prostate cancer in the past several years (9–11), we put a special emphasis on data published in the last year after these prior reviews were written that suggest that obesity may reduce the Risk of being diagnosed with nonaggressive disease and simultaneously may increase the Risk of being diagnosed with aggressive disease.

Finally, we will conclude with a very brief description of some of the hormonal sequelae of obesity and their potential relation to prostate cancer, with particular attention to testosterone and other hormones that are altered in obese men (i.e., estradiol, insulin, IGF-1, leptin, and adiponectin). We have chosen to provide a lengthier discussion regarding testosterone, because of the potentially very important role that testosterone plays in prostate cancer development. In addition, given that obesity is associated with decreased serum concentrations of testosterone, understanding the role of testosterone in tumor development and progression is essential to better understanding the association between obesity and prostate cancer. For more detailed review articles regarding sex hormones or hormones in general and their relation to prostate cancer, we recommend the following reviews (12–14). In addition, the role of diet and physical activity is beyond the scope of this review, and the reader is referred to the following reviews (15–17).

**OBESITY AND RISK OF PROSTATE CANCER DIAGNOSIS**

Prior studies examining the relation between adult body mass index and risk of developing prostate cancer have reported mixed results. Several cohort studies found that increased body mass index in adulthood was associated with an increased risk of developing prostate cancer (18–21). However, among these studies, only one (19) showed increased risk for men in the highest body mass index category of 27.6 or more versus 22.5 or less kg/m² (relative risk (RR) = 2.2, 95 percent confidence interval (CI): 1.1, 4.7), and another study (20) found only a weak, albeit statistically significant association with prostate cancer risk for those with a body mass index of 30 or more versus 18.5–24.99 kg/m² (RR = 1.09, 95 percent CI: 1.04, 1.15). On the other hand, numerous prospective cohort studies have found no association between adult body mass index and prostate
cancer risk (22–25). More recently, a prospective cohort study from the United States found an inverse association between obesity and prostate cancer diagnosis, but only among men aged less than 60 years or those with a family history of the disease (26). Given these conflicting results, a recent meta-analysis of 22 prospective cohort studies examined this issue and concluded that obesity was associated with a significant, but weak increased risk of prostate cancer (for each 5 kg/m²: RR = 1.06, 95 percent CI: 1.03, 1.10) (27). Interestingly, when studies that examined localized and advanced disease were examined separately, increasing body mass index was associated with increased risk of only advanced disease (for each 5 kg/m²: RR = 1.12, 95 percent CI: 1.01, 1.23) and not localized disease (for each 5 kg/m²: RR = 0.96, 95 percent CI: 0.89, 1.03).

Since the publication of this meta-analysis, three recent large prospective studies examined the association between obesity and prostate cancer risk separately by stage and/or grade at diagnosis. Interestingly, in all three studies, obesity was positively associated with increased risk of high-grade or high-stage disease and inversely associated with low-grade and low-stage disease (28–30). Thus, there appears to be consensus, at least among these most recent studies, that obesity may reduce the risk of being diagnosed with nonaggressive disease while simultaneously obesity may promote the risk of developing aggressive disease. Possible reasons for this disparate effect of obesity on the risk of aggressive and nonaggressive disease are discussed in more detail below.

Given the long, protracted course of prostate cancer, it is felt that perhaps events that occur earlier in life may predispose to prostate cancer later in life. As such, examination of adulthood body mass index may have missed the window when excess body mass index and all its sequelae would have affected prostate cancer risk. To address this issue, several studies examined the relation between prostate cancer risk and obesity earlier in life (age 10–30). Analogous to the findings when adulthood body mass index was examined, these studies have demonstrated mixed results, with some studies finding a direct relation between body mass index early in life (ages 10–30 years) and the risk for developing prostate cancer (22, 31), while others found that obesity in early life at age 5 (32) and 20 (33) years was protective for developing prostate cancer. Thus, given the limited data for body mass index at younger ages and the fact that these data appear to conflict, further research is needed to better assess the association between early life body mass index and prostate cancer risk.

OBESITY AND DIFFICULTIES IN PROSTATE CANCER DETECTION

As noted above, the consensus appears to be that obesity while promoting aggressive and fatal disease actually is associated with a modest reduction in the diagnosis of localized, low-grade disease. One potential explanation is that obese men have lower levels of testosterone that may biologically prevent prostate cancer. However, there is increasing evidence that an alternative though not mutually exclusive explanation may be involved. Specifically, several recent studies have suggested that prostate cancer may be more difficult to detect among obese men.

First, anecdotally, a thorough digital rectal examination, an important part of prostate cancer screening, is more difficult to perform in obese men. Thus, it is conceivable that physicians may be missing prostate cancers in obese men that would have otherwise been detected on examination. Second, the other component of prostate cancer screening besides a thorough rectal examination involves measuring the serum concentration of PSA, a protein produced by both benign and malignant cells of the prostate. It is well established that increased serum concentrations of PSA are associated with increased risk of having an existing prostate cancer. However, there is no cutoff value above which prostate cancer is guaranteed to be present or below which no prostate cancer exists (34). Therefore, physicians ever since the late 1980s and early 1990s, at least in the United States, have used an elevated PSA as a sign that a man may have prostate cancer and a reason to perform a prostate needle biopsy. Recently, multiple reports have found that obese men have lower PSA values (35–40). It is unknown why obese men have lower PSA values. One possibility is that the lower testosterone levels among obese men stimulate less PSA production (PSA production is under direct testosterone control) (41). Alternatively, obese men have greater plasma volume. Given that PSA is normally released in seminal fluid and only as a by-product leaks at low levels into the serum, greater plasma volume in obese men could result in hemodilution, thus lowering the serum concentration of PSA (42). Regardless of the reason, lower PSA concentrations would make obese men less likely to have an abnormal PSA test and therefore be less likely to be referred for a prostate needle biopsy. Fewer biopsies performed would mean fewer cancers detected. Finally, multiple studies have suggested that obese men have larger sized prostates (43–45). Most prostate cancers detected in the United States are so small that they can not be seen using conventional imaging modalities. As such, prostate needle biopsy is most analogous to looking for a needle in a haystack. Thus, it is easy to imagine that prostatic enlargement (larger haystack) would make detection of an existing cancer (needle) less likely, given an equally sized tumor and an equal number of biopsy cores obtained (46, 47). Ultimately, combining the difficulty in performing a thorough rectal examination, lower PSA concentrations, and prostatic enlargement would represent an inherent bias against detecting cancers among obese men. Consequently, if cancers are harder to detect among obese men, this may lead to delayed diagnosis and subsequently later stage disease at the time of diagnosis.

To illustrate this potential for bias, we highlight the results from two studies that examined the same cohort of 787 men undergoing prostate needle biopsy to rule out prostate cancer. In the first study, the authors found on crude analysis that obese men had a lower risk of being diagnosed with prostate cancer on biopsy (48). However, upon a more thorough review of the patients’ characteristics, it was found that obese men were less likely to have an abnormal rectal examination and had lower PSA values and larger prostates (49). When these factors were accounted for, obese men had
a higher risk of prostate cancer detection and, among men with cancer, obese men had higher grade tumors (49).

It is important to point out that this inherent bias against detecting cancers in obese men remains a hypothesis and a relatively new hypothesis. As such, it is unclear to what degree this bias could and does explain any of the observed epidemiologic literature from the last 15 years. However, it is our opinion that bias is very plausible and would have a major influence on the interpretation of the recent literature about obesity and prostate cancer. Moreover, this bias, if real, would help to explain the recently observed inverse association between obesity and low-stage, low-grade prostate cancer (28, 30). Furthermore, this bias would be expected to lead to a delay in disease diagnosis, which could contribute to the link between obesity and more advanced disease at diagnosis (28, 30) as well as potentially explain poorer outcomes after treatment. Of note, however, the inverse association between obesity and low-grade disease and the positive association with high-grade disease were observed in a series where all men underwent biopsy (29).

Thus, although prostate size differences between obese and normal weight men potentially remain, it is unlikely that lower PSA values resulting in differential biopsy rates alone can fully explain the disparate effect of obesity on prostate cancer risk by disease aggressiveness.

**OBESITY AND ONCOLOGIC OUTCOMES AFTER TREATMENT**

Among men with newly diagnosed prostate cancer, nearly 90 percent will undergo some form of curative therapy (50). This usually entails either surgery to remove the prostate (i.e., radical prostatectomy) or some form of radiation therapy: either seed implant (i.e., brachytherapy) or external beam radiation therapy. Outcomes among obese men following treatment have been most extensively studied among the select subset of men undergoing surgery.

Multiple studies found that, among men undergoing surgery for early stage prostate cancer, those with increased body mass index had higher grade (51–53) and higher stage (54) disease. In regard to surgical outcomes (i.e., likelihood of cancer recurrence), this has been addressed by 10 studies to date, with eight of the 10 studies (52, 53, 55–60) finding higher cancer recurrence rates among obese men and only two studies (61, 62) finding no association between body mass index and cancer recurrence. Moreover, all three studies that involved multicenter data found increased risk of cancer recurrence among obese men (52, 53, 58).

One note about surgical series deserves special mention. Keeping in mind that PSA is produced essentially only by the prostate and that surgery removes the entire prostate, slight elevations in PSA after surgery are taken as a sign of cancer recurrence. However, one study found that, among obese men, even in very experienced hands, the surgeons were more likely to cut into the prostate during the surgery, a phenomenon called capsular incision and a sign of technically inferior operation (63). This raises the possibility that technical challenges in operating on obese men result in a less than adequate tumor excision, thus contributing to poorer outcomes among obese men. While this is certainly possible, another study examined men in whom the entire prostate was removed and the cancer was completely confined to the prostate (64). Even in that setting, obese men had an increased risk of cancer recurrence, suggesting that technical issues cannot explain all of the increased risk of recurrence noted among obese men.

The other common method, besides surgery, to treat early stage prostate cancer involves radiation therapy. To date, only two studies have examined outcomes among obese men undergoing radiation therapy. In the first study, the authors found among men treated with brachytherapy that there was no association between body mass index and cancer recurrence (65). Alternatively, in the second study, the authors noted that, among men treated with external beam radiation therapy, higher body mass index was associated with increased risk for cancer recurrence and development of metastasis (66). Given the limited amount of data, it is unclear whether differences between these two studies represent differences in patient selection factors, the differential impact of brachytherapy and radiation therapy on obesity-related tumor biology, or some other alternative explanation.

In summary, with few exceptions, obese men undergoing treatment for early stage prostate cancer appear to have a greater risk of cancer recurrence than do their thinner counterparts. While technical issues related to treatment of obese men likely contribute to this discrepancy in outcome, they cannot fully account for it.

**OBESITY AND RISK OF DEATH FROM PROSTATE CANCER**

While the relation between obesity and prostate cancer incidence is controversial, the relation between obesity and mortality from prostate cancer is much better established. Epidemiologic data from prospective cohort studies have relatively consistently found a statistically significant positive association between obesity (either increased body mass index or greater than desirable weight) and risk of death from prostate cancer (18, 67–70). Several large prospective cohort studies deserve particular attention. In 1959 and again in 1982, the American Cancer Society enrolled a cohort of participants for longitudinal studies on cancer, known as the Cancer Prevention Study (CPS) I and II, respectively. Men were then followed for 13 years in CPS-I and 14 years in CPS-II. Together, these studies followed 816,268 men, during which time there were 5,212 prostate cancer deaths. Both CPS-I and CPS-II reported that obese men (body mass index: >30 kg/m²) were significantly more likely to die from prostate cancer with a 27 percent and a 21 percent increased risk of prostate cancer death relative to normal weight men (body mass index: <25 kg/m²), respectively (67). More details regarding the CPS-II cohort were published, which showed that severely obese men (body mass index: >35 kg/m²) were at even greater risk of death from prostate cancer (34 percent higher risk) relative to normal weight men (68). Thus, the risk of death from prostate cancer in CPS-I and CPS-II appeared to increase with increasing body mass index above “normal.” A prospective
study of 135,000 construction workers in Sweden found similar results, in that men in the highest body mass index category were 40 percent more likely to die from prostate cancer than were men in the lowest body mass index category (18). Finally, a study from Scotland found that increased body mass index among college students was associated with a 49 percent increased risk of prostate cancer death, suggesting that events involved in prostate carcinogenesis and progression may occur years before actual tumor development, though the confidence interval in this study was wide and included one (95 percent CI: 0.54, 4.12) (71). Therefore, there appears to be near uniform consensus among multiple studies involving over a million men followed prospectively that obesity is associated with increased risk for prostate cancer death.

TESTOSTERONE AND PROSTATE CANCER

As discussed above, one of the potential explanations for the inverse association between obesity and risk of being diagnosed with prostate cancer relates to technical issues involved in prostate cancer detection. An alternative explanation revolves around a biologic link between obesity and reduced prostate cancer risk. Specifically, obese men are known to have increased serum estradiol levels due to peripheral conversion of testosterone to estradiol by aromatase in adipocytes (72). In turn, this estradiol results in feedback inhibition at the level of the pituitary, resulting in decreased bioactive (i.e., free) testosterone levels (73). These alterations in sex steroids that accompany obesity may have profound consequences for prostate cancer development and progression.

Androgens (i.e., testosterone and the more potent dihydrotestosterone) are necessary for prostate growth, maturation, and differentiation (74). In patients with 5-alpha reductase type II deficiency, and thus who cannot convert testosterone to dihydrotestosterone, the prostate develops only rudimentarily (75). Among men with prostate cancer, surgical or medical castration results in dramatic tumor involution and regression (76). These clinical observations would suggest that androgens likely play a key role in prostate cancer development. While this is probably true, the exact role that androgens play is unclear because of the fact that epidemiologic studies regarding the association between serum androgen levels and prostate cancer risk are mostly null. Specifically, nearly all prospective cohort studies found no significant association between prediagnostic serum testosterone levels and prostate cancer risk (77), though one study did find a positive association, albeit only after adjustment for serum levels of sex hormone binding globulin (78). However, it is worth noting that, analogous to the discussion above regarding when is the optimal time to measure obesity in terms of evaluating prostate cancer risk, the optimal time in a man’s lifetime to measure prediagnostic testosterone levels for subsequent prostate cancer risk is also unknown.

There are potentially a couple of reasons that studies to date of circulating serum androgen levels and prostate cancer risk are largely null. First, most studies examined all prostate cancer together, without trying to separate aggressive from nonaggressive cancers. One method to separate these is to use the grade of the cancer. The higher the grade the cancer is, the more aggressively the cancer will behave. However, tumor grade also correlates with tumor differentiation status. Thus, given that testosterone helps to promote normal prostate epithelium differentiation, it is reasonable to think that lower testosterone activity may also affect tumor differentiation. Indeed, multiple studies have found that, among men with prostate cancer, decreased serum testosterone levels have been associated with more advanced and poorly differentiated tumors at presentation (79–82). Moreover, two recent prospective cohort studies both concluded that lower serum androgen concentrations affected not total prostate cancer risk but, rather, the risk of high-grade, more poorly differentiated disease (83, 84). Specifically, both studies found that lower prediagnostic serum androgen levels (i.e., similar to obesity) were associated with increased risk for future diagnosis of high-grade prostate cancer. It has even been suggested that maintaining a normal serum testosterone level may help to prevent prostate cancer (85), though this is a very controversial point. Thus, it is possible that the lower free testosterone levels found in obese men may predispose them to developing more poorly differentiated, advanced prostate cancers and partly explain the higher mortality of prostate cancer among obese men, while at the same time explaining the lower risk of indolent, low-stage, low-grade cancers.

Another potential issue that could bias the prior studies on circulating androgens and prostate cancer toward the null is the fact that the vast majority of men in these studies had “normal” testosterone levels. Thus, it is possible that more extreme differences in androgen activity may result in greater differences in prostate cancer development. Indeed, a recent prospective trial highlights this issue (86). In this study, healthy men were randomized for 7 years to receive placebo or finasteride, a 5-alpha reductase inhibitor, which blocks the conversion of testosterone to dihydrotestosterone and thus dramatically lowers androgen activity. At the end of the study, it was noted that men on finasteride had a significantly reduced risk of being diagnosed with prostate cancer but had an absolute increase in the risk of being diagnosed with high-grade prostate cancer.

OTHER HORMONAL CHANGES ASSOCIATED WITH OBESITY

Beyond changes in androgens, obesity is associated with increased serum levels of estradiol, insulin, and leptin and decreased levels of adiponectin. In addition, some (87, 88), but not all (89), studies have found that obesity is associated with increased free or bioactive IGF-1 concentrations. The relevance of these changes is that all of these steroid and peptide hormones have in some studies been linked with prostate cancer.

With regard to estradiol, when combined with testosterone in animal models, it helps to promote prostate tumors (90–92). Second, men in Asia who consume a high soy diet (soy is a phytoestrogen) have a reduced risk of prostate cancer (93). Finally, a small placebo-controlled phase II
FUTURE DIRECTIONS

It is becoming increasingly clear that adult obesity is associated with reduced risk of being diagnosed with prostate cancer but a greater risk of developing aggressive/fatal prostate cancer. However, there are many unresolved issues. To what degree are these epidemiologic observations due to difficulty in prostate cancer detection among obese men versus having a true “biologic” explanation? When is the critical time in a man’s life that obesity and its sequelae have the greatest impact on prostate cancer risk? What are these observations telling us in terms of the role that diet and various hormones play in prostate cancer development? Specifically, can pharmacologic or lifestyle intervention to alter some or all of these metabolic pathways affect the risk of having prostate cancer, particularly aggressive prostate cancer? And finally, though limited evidence suggests that adult pre-diagnostic weight gain may increase the risk for cancer recurrence after treatment (59) or development of fatal prostate cancer (28) while weight loss may reduce the risk of nonmetastatic, aggressive disease (30), once diagnosed with prostate cancer, can an obese man lose weight and improve his outcomes and better his chances of survival?

Although the answers to the above questions are as yet unknown, we would suggest that future research should look at not simply body mass index but better correlates of adiposity. It is known that body mass index is only an approximate indicator of adiposity. Therefore, better defining adiposity may expose clearer and perhaps new associations with prostate cancer and other diseases as well. In addition, not all adiposity is created equal. Thus, future research needs to evaluate the role of central versus peripheral adiposity in epidemiologic studies. Finally, research should investigate the role of not just obesity at one point in adulthood but rather lifelong obesity. Indeed, events early in life such as childhood obesity and obtained adult height (27) both appear to influence prostate cancer biology. Therefore, perhaps in a manner analogous to smoking where we

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discuss pack-years (i.e., number of cigarette packages smoked per year multiplied by the number of years of smoking), we should be discussing body mass index-years or area under the age-adiposity curve. Moreover, these age-adiposity curves may have to be broken into different times of life. For example, a high area under the age-adiposity curve during adolescence and childhood may be protective in that it delays puberty and thus delays prostate maturation, whereas a high area under the age-adiposity curve during adulthood may promote a mature prostate into developing an aggressive cancer. Perhaps this measure, which includes duration of obesity as well as the degree of adiposity, may better reflect the long-term sequelae of obesity and help us understand the biologic links between obesity and prostate cancer. Only once these molecular links are identified can we begin to design rational approaches for prostate cancer prevention. Moreover, while future research will hopefully elucidate these molecular pathways, continued research is needed to comprehend to what degree epidemiologic observations are driven by technical difficulty in adequately detecting prostate cancers among obese men.

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