Obesity and Prostate Cancer: A Growing Problem

Commentary on Strom et al., p. 6889

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Obesity is an epidemic in American society with approximately one in three adults in the United States being considered obese (1). This compares to “only” one in six adults being considered obese 20 years ago (Fig. 1; ref. 1). The exact reasons for this dramatic increase in obesity prevalence in the last 20 years likely include alterations in diet and amount of physical activity. Obesity is associated with numerous chronic medical problems including coronary artery disease, hypertension, and diabetes (2). In a landmark study, Calle et al. from the American Cancer Society enrolled over 900,000 adults who were free of cancer at the time of study enrollment in 1982 (3). The study participants were then followed for 16 years to assess for risk of death from cancer. The authors found that higher body mass index (BMI) was positively associated with risk of death from 12 different types of cancer among men, including prostate cancer. Category I obese men (BMI, 30.0-34.9 kg/m²) were 20% more likely to die from prostate cancer than normal weight men (BMI, 18.5-24.9 kg/m²), whereas men who were category II obese (BMI, 35.0-39.9 kg/m²) were 34% more likely to die from prostate cancer. Similar observations have been made in multiple other prospective cohort studies (4, 5), including a very similar study reported by Rodríguez et al. also from the American Cancer Society, which enrolled over 400,000 men in 1959 and followed them through to 1972 (4). Collectively, these studies have enrolled over 1,000,000 men in prospective cohort studies and found relatively strong evidence to suggest that obese men are at increased risk for prostate cancer death. In terms of early-stage disease, several reports, including the study by Strom et al. in this issue, have consistently suggested that men with a higher BMI are at increased risk for biochemical progression following radical prostatectomy (6–9), although the association did not reach statistical significance in all studies (8, 9).

Why is obesity associated with more aggressive prostate cancer (e.g., greater risk of prostate cancer death and greater risk of progression after surgery)? Undoubtedly, the reasons are complex and multifactorial. Therefore, rather than trying to cover every possible explanation for this apparent association, I have selected just a few leading hypotheses, keeping in mind that these hypotheses are not mutually exclusive.

One hypothesis is that the way we screen for and treat prostate cancer is biased against obese men. Viewed alternatively, it is possible that it may be harder to find a cancer in an obese man and even when we find the cancer the adiposity may make treatment of the cancer more difficult. First, anecdotally it is harder to perform a proper digital rectal examination in an obese man and thus it may be possible to miss a cancer. Second, obese men may have larger prostate sizes making it harder to feel a cancer and harder to find the cancer at the time of biopsy (10). The analogy that comes to mind is, if doing a prostate biopsy looking for cancer is like searching for a needle in a haystack, then the larger the haystack, the harder to find the needle. Third, despite larger prostate sizes, obese men may have lower serum prostate-specific antigen (PSA) values, presumably due to lower testosterone and higher estradiol levels among obese men (11, 12). Lower PSA concentrations would make obese men less likely to have an abnormal PSA test and undergo biopsy resulting in fewer cancers detected, such that the cancers that were detected would be more advanced. The combination of these three factors may result in obese men presenting at a later stage of disease than nonobese men. In addition, there is the added bias that surgery is more difficult to do among obese men resulting in a greater risk of a positive surgical margins (6) and capsular incision (inadvertent incision into the prostate at the time of radical prostatectomy; ref. 13), suggesting that surgery may be less efficacious among obese men. Ultimately, the net result of these biases would be for obese men to present with more advanced disease and even adjusting for this to have a worse outcome after radical prostatectomy.

It is important to note that this “nonbiological” detection bias hypothesis is in part based upon the association between obesity and larger prostate size and lower serum PSA values, both of which are biological phenomena. Moreover, the positive association between obesity and risk of death from prostate cancer, as noted by Rodríguez et al., was observed in men from the 1950s and 1960s, long before PSA screening (4). In addition, during that time, not only were patients rarely diagnosed early enough to justify surgery, but surgery itself was rarely done due to excess morbidity. Thus, detection bias issues related to PSA or less efficacious surgery cannot solely explain the association between obesity and risk of prostate cancer death. Instead, some truly “biological” explanation is warranted to completely understand the association between obesity and aggressive prostate cancer. Various “biological” explanations have been given including...
alterations in serum hormone concentrations (e.g., testosterone, estrogen, and insulin), diet, and lack of physical activity. As noted above, likely all of these various factors play a role, at least to some degree.

Obesity is associated with decreased free testosterone levels (14). Testosterone is a key prostate growth factor. However, recent data from retrospective studies suggest that testosterone may exert a differentiating effect on prostate cancer and decreased serum testosterone levels have been associated with more advanced and poorly differentiated tumors at presentation (15, 16). Viewed alternatively, only aggressive partially androgen-insensitive cancers can grow in a low-androgen “hostile environment.” Either way, the cancers that develop in men with low testosterone (e.g., obese men) seem more aggressive. Interestingly, a recent prospective cohort study found that despite no overall association between serum testosterone levels and prostate cancer development and progression is unclear, but recent animal and experimental studies suggest that elevated estradiol levels may play an important role in testosterone-induced carcinogenesis. Studies in mice with genetically altered aromatase or estrogen receptor expression found that estradiol combined with testosterone plays an important role in regulating proliferation and apoptosis of prostate cells (20, 21). In several experimental animal models, the coadministration of testosterone with estrogens greatly enhances tumorigenesis relative to treatment with testosterone alone (22, 23). A diet high in phytoestrogens has been suggested as one of the key potential mechanisms for the lower incidence of prostate cancer among men in Asia (24).

Fig. 1. The percentage of U.S. adults ages ≥20 years who are obese (BMI ≥30 kg/m²) by state, (A) in 1990 and (B) in 2003 (60).
Finally, a recent preliminary small study found that the selective estrogen receptor modulator, toremifene, may prevent the development of prostate cancers in some men at high-risk for prostate cancer (25), although further study is needed to confirm this finding. Based on these observations, it is certainly possible that elevated levels of estradiol in obese men may enhance the growth promoting effect of testosterone on prostate cancer and result in more cancer and possibly more aggressive cancers. For more detailed review articles regarding sex hormones (e.g., testosterone and estradiol) and their relationship to prostate cancer, I recommend the following reviews (26–28).

Beyond alterations in the sex steroid hormones of testosterone and estradiol, obesity is associated with altered levels of several other serum hormones, including insulin, leptin, and adiponectin. Insulin is a direct mitogen for in vitro prostate growth (29). Several studies found that fasting serum insulin (30), serum glucose (31), or insulin resistance (32) were positively associated with prostate cancer risk. Additional evidence regarding the possible role of insulin in prostate cancer biology comes from epidemiologic studies of men with diabetes. Diabetes results from inadequate insulin secretion, due to lack of pancreatic β-cell reserve. In men with diabetes, there is a progressive loss of β-cell function and over time men develop hyperinsulinemia (33). Whereas not a universal finding in all studies (34), most prospective cohort studies (35–38) as well as a recent meta-analysis (39) found that diabetes was associated with a decreased prostate cancer risk, supporting the role of insulin in promoting prostate cancer development and or growth.

Increasing evidence suggests that adipose tissue not only stores excess fat but also can function as an endocrine organ. Adipocytes produce multiple polypeptide hormones, of which leptin is the best characterized. The normal physiologic role of leptin is to signal the brain that there are sufficient fat stores, which in turn results in curbing appetite (40). In terms of prostate cancer, leptin stimulates the in vitro growth of androgen-insensitive but not androgen-sensitive prostate cancer cells (41). The data relating serum leptin levels to prostate cancer risk is mixed with one study showing a positive association (42) but others showing no significant association (30, 43). Among men with prostate cancer, two studies found that increased serum leptin concentrations were associated with larger, higher-grade, and more advanced tumors (44, 45), although a third study found no association between leptin concentrations and pathologic tumor stage (46). Interestingly, a recent study found that a particular polymorphism within the leptin gene that is associated with increased leptin production and secretion was associated with increased risk of prostate cancer, particularly advanced disease (47).

Adiponectin is a polypeptide hormone that is also produced exclusively by adipocytes. Although less well characterized than leptin, it seems to be involved in energy homeostasis. Contrary to leptin, adiponectin levels are lower among obese men. Adiponectin has been shown to have antitumor activity via inhibition of angiogenesis (48). Only two studies have examined serum adiponectin levels among men with prostate cancer and both studies found that lower adiponectin levels were associated with higher-grade and more advanced disease (49, 50), although in one study, the association was limited to overweight and obese men (50).

Another facet of obesity that may link it with prostate cancer is diet. Obesity is highly correlated with dietary intake in terms of both the number of calories and the amount of dietary fat intake diet (51). In animal models, a high fat diet promotes androgen-sensitive prostate cancer growth and can promote progression from androgen-sensitive to androgen-insensitive growth (52–54). Globally, prostate cancer incidence and mortality rates are associated with a Western lifestyle and diet, although whether this reflects increased fat intake or decreased intake of various protective products such as soy and lycopene is unclear (55). Moreover, as men in underdeveloped nations adopt a more Western lifestyle and diet the incidence and mortality from prostate cancer has increased (55). Notably, in the study in this issue by Strom et al., men who gained the most weight from age 25 until diagnosis (e.g., were in positive calorie balance) were at increased risk for progression. This observation mirrors data from a prior prospective cohort study (56), which found that energy intake was positively associated with metastatic or fatal prostate cancer in certain subsets of men. In addition, animal studies have found that caloric restriction delays prostate cancer growth (57). These findings highlight that not just the type of food eaten but the amount of food consumed may affect prostate cancer growth. Ultimately, diet is a very complex issue involving type of food consumed (e.g., fat versus carbohydrates versus proteins; monounsaturated versus polyunsaturated versus saturated fat; animal meat versus fruits and vegetables, etc.) and amount of food consumed. However, given the global association between a Western diet and prostate cancer incidence and mortality, it is hard to argue that diet does not play some role in prostate cancer development and or progression.

Ultimately, obesity is a growing problem in Western society. The association between obesity and risk of death from prostate cancer has been firmly shown in multiple prospective cohort studies. Recently, obesity has also been linked with increased risk of biochemical progression following radical prostatectomy. The link between obesity and aggressive prostate cancer is likely complex and involves multiple different mechanisms. However, through a better understanding of how these pathways promote aggressive cancer growth among obese men, we will gain valuable insights into the etiology of prostate cancer in general. It is anticipated that this better understanding will lead to new diagnostic measures, prognostic tools, and therapeutic maneuvers to reduce prostate cancer burden. In the meantime, the best advice is to exercise regularly, eat a balanced diet, and to achieve and maintain a healthy weight. We know that this advice will help reduce the risk of heart disease, the overall number one cause of death (58). In time, I believe this advice will also be shown to help prevent prostate cancer, particularly aggressive prostate cancer. Finally, preliminary evidence suggests that this approach may reduce the risk of breast cancer recurrence (59), a cancer very closely related to prostate cancer. I believe now is the time to start asking whether such an approach can improve outcomes for men with prostate cancer.

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References

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