Examining the Relationship Between Obesity and Prostate Cancer

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Affecting over 30% of the population, obesity is an epidemic in the United States and is associated with multiple chronic medical problems. Obesity is also associated with numerous hormonal changes, many of which have been implicated in prostate cancer development and progression. Although, on the whole, controversy exists over whether obesity increases the risk of prostate cancer, data strongly suggest that obesity is a significant risk factor for prostate cancer death. In this review, we discuss the epidemiologic data surrounding obesity and prostate cancer. We also discuss some of the sequelae of obesity and their relationships with prostate cancer, including alterations in insulin, the insulin-like growth factor axis, and leptin levels; insulin resistance; and diabetes. Although a complete overview of all the various dietary and lifestyle factors that are associated with obesity and prostate cancer risk is beyond the scope of this review, we discuss data concerning the relationship between a high-fat diet and prostate cancer.
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Key words: Body mass index • Dietary fat • Insulin-like growth factor • Leptin • Obesity • Prostate cancer

Obesity is a major health problem that affects more than 30% of adults in the United States.[1] Every state has seen a dramatic increase in the prevalence of obesity over the past 10 years (Figures 1 and 2).[2] Obesity is associated with the development of multiple chronic diseases, including coronary artery disease, hypertension, and diabetes.[3-5] Obesity has also been linked to several types of cancer, including that of the breast and colon.[6] A recent study of 900,000 per-

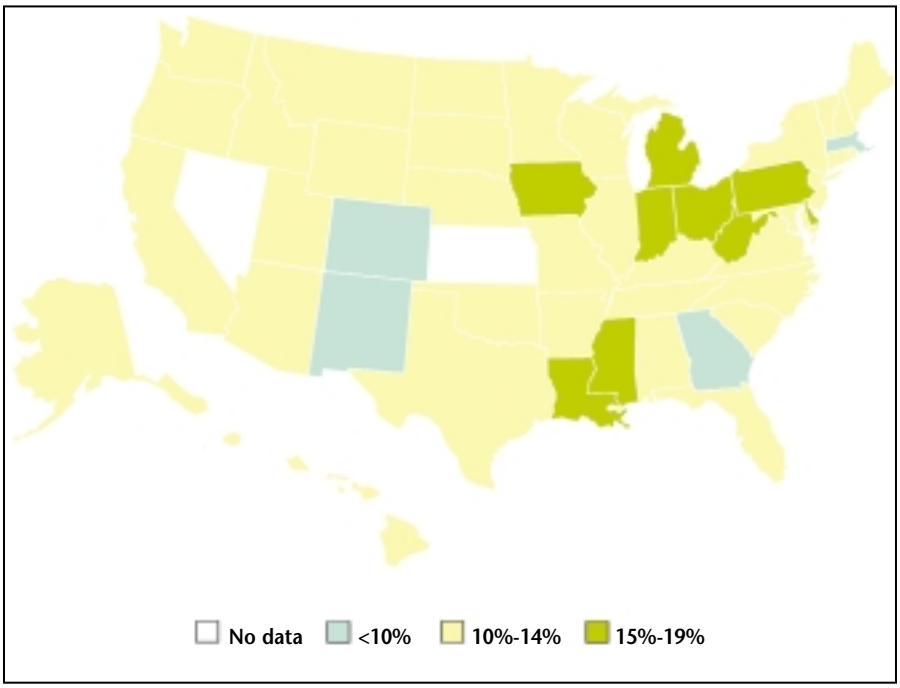


Figure 1. *The percentage of US adults aged 20 years or older who are obese (BMI >30 kg/m^2) by state in 1991. Data from Ahluwalia IB et al.* MMWR Surveill Summ. *2003;52:1-80.*[2]

sons found that obese patients were more likely to die from a number of cancers, including prostate cancer.[7] However, studies of obesity and prostate cancer are complicated by the fact that obesity is associated not only with excess body fat but also with altered serum levels of numerous hormones, including testosterone, estrogen, insulin, insulin-like growth factor (IGF)-1, and leptin, all of which have to some degree been linked to prostate cancer. In addition, obesity is highly correlated with dietary intake in terms of the number of calories as well as the amount of dietary fat, both of which have been linked to cancer.[8]

Whereas some studies have examined obesity in and of itself (excess body weight), others have examined various components that are disregulated in obesity. A complete review of all the various sequelae of obesity (Figure 3) and their relationships to prostate cancer is beyond the scope of this review. Therefore, we focus primarily on the data that directly link obesity to prostate cancer. We also briefly describe some of the factors related to obesity and their relationships with prostate cancer, focusing on insulin, the IGF axis, leptin, and dietary fat. More detailed review articles regarding sex hormones (testosterone and estrogen) or hormones in general and their relationships to prostate cancer can be found in the literature.[9-11]

Before undertaking a review of the literature regarding obesity and prostate cancer, the term "obesity" must be defined. Webster's dictionary defines obesity as "a condition characterized by excessive bodily fat."[12] One of the most common definitions of obesity is an increased body mass index (BMI), which is calculated by dividing weight in kilograms by height in meters squared. Both the World Health Organization and the National Institutes of Health define overweight as a BMI of greater than 25 kg/m^2 and obesity as a BMI of greater than 30 kg/m^2. Although it is easily determined, BMI has its limitations. For example, body composition, such as whether someone is particularly muscular or thick-boned, is not factored into BMI calculations. Therefore, alternative measurements and definitions of obesity, including waist-to-hip ratio (WHR), percent body fat, skinfold thickness, crude weight, and lean body mass, have been used in various studies.[13]

Increased BMI and Risk of Prostate Cancer

The epidemiologic evidence linking an increased adult BMI to an increased risk of prostate cancer is controversial. Although several large studies have found an increased BMI in adulthood to be associated with an increased risk of the development of prostate cancer,[14-20] others have shown no such association.[21-29] Interestingly, a recent study from Norway, which followed 950,000 men for an average of 21 years, found that a BMI of greater than 30 kg/m^2 increased the risk of prostate cancer by only 9%.[30] However, obese men aged 50 to 59 years at study completion had a 58% increased risk of prostate cancer; no other age group had a statistically significant increased risk. Thus, an interaction between age and obesity could explain why some studies have found an increased risk whereas others have found no relationship between obesity and prostate cancer risk. Moreover, Giovannucci and colleagues,[31] using data from the Health Professionals Follow-up Study, an ongoing prospective study of more than 50,000 male US health professionals, which began enrollment in 1986, found that an increased BMI was associated with a decreased risk of prostate cancer among men younger than 60 years or those with

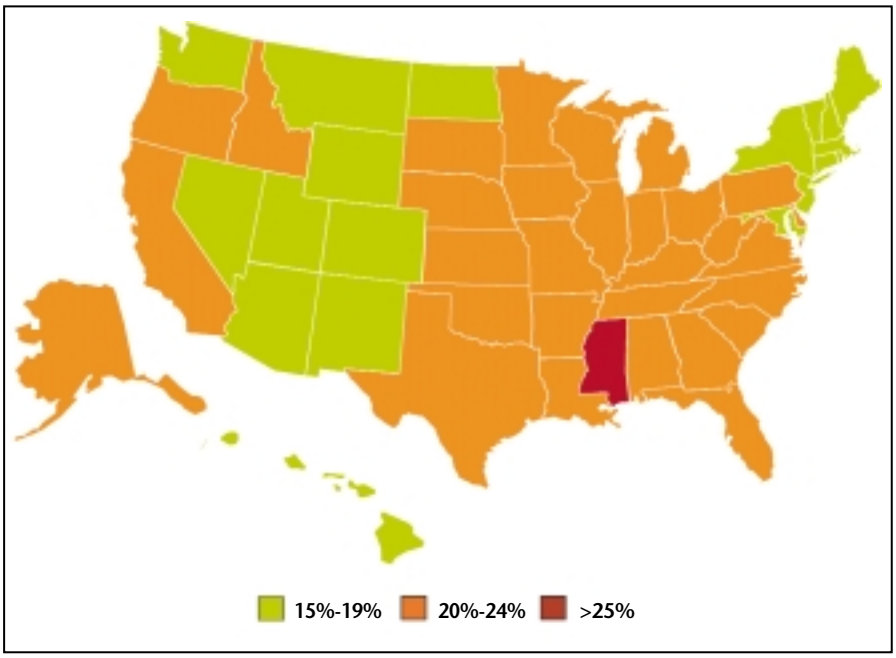


Figure 2. *The percentage of US adults aged 20 years or older who are obese (BMI >30 kg/m²) by state in 2001. Data from Ahluwalia IB et al.* MMWR Surveill Summ. *2003;52:1-80.*[2]

a family history of the disease. In this study, obesity was not related to prostate cancer risk among older men. Although the relationship between obesity and prostate cancer risk was opposite from that seen in the Norwegian study, both studies suggest that a significant interaction exists among age, obesity, and prostate cancer risk.

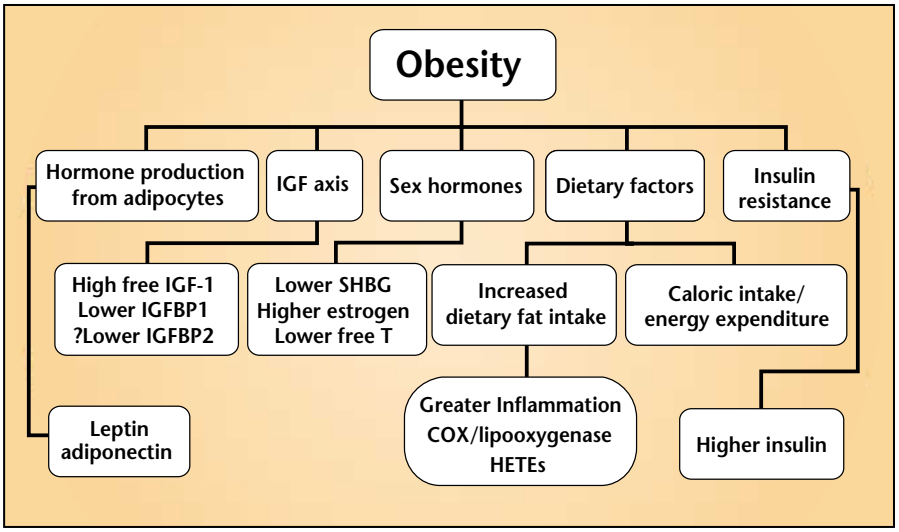
Based on their findings, Giovannucci and colleagues[31] argued that tumors in younger men and those with a family history of prostate cancer may be driven by increased androgens and, thus, the lower androgen levels seen in men with obesity may have been protective against prostate cancer.[32] Interestingly, whereas the authors found that obesity was protective against prostate cancer in general, they found no relationship between obesity and advanced disease, suggesting that, although obesity protects against early disease, it provides no protection against advanced disease. Similarly, several of the studies that did find a significant association between increased BMI and risk of prostate cancer also found that the risk of advanced disease was even stronger than the risk of prostate cancer in general.[15,17]

Given the protracted course of prostate cancer, it is thought that events that occur earlier in life may predispose to prostate cancer later in life. Thus, examination of adulthood BMI may miss the window during which increased BMI and its sequelae affect prostate cancer risk. To address this issue, several studies examined the relationship between prostate cancer risk and obesity earlier in life (ages 10-20 years). These studies, like those examining adulthood BMI, have demonstrated mixed results: some studies have found a direct relationship between BMI early in life and the risk of prostate cancer,[22] whereas others have found increased BMI to be protective against prostate cancer.[21]

Increased BMI and Oncologic Outcomes After Primary Therapy

Several studies have found that, at the time of radical prostatectomy, men with an increased BMI had higher-grade and/or higher-stage disease.[33-35] Two recent studies utilized large multi-institutional databases of multi-ethnic patients to address whether increased BMI was associated with higher biochemical failure rates following radical prostatectomy

Figure 3. *Obesity and its related sequelae. IGF, insulin-like growth factor; IGFBP, IGF-binding protein; SHBG, sex-hormone-binding globulin; COX, cyclooxygenase; HETE, hydroxyeicosatetraenoic acid.*



(Figure 4).[36,37] Both studies concluded that obese men were at increased risk of biochemical failure. Interestingly, both studies found that black men were more likely to be obese, which may explain, in part, the higher rate of mortality from prostate cancer among black men.[38] Further studies are needed to determine whether obese men are at increased risk for failure following other forms of primary therapy, such as external-beam radiation therapy and brachytherapy.

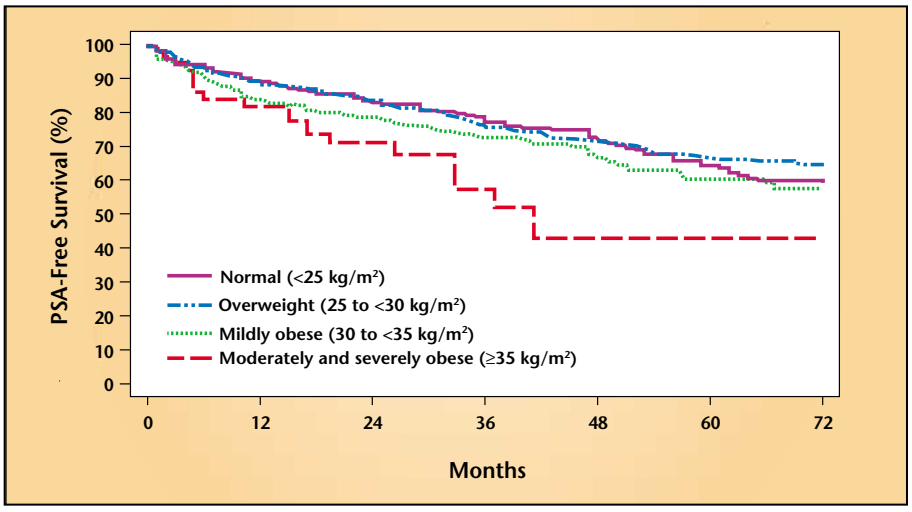


Figure 4. *Actuarial risk of biochemical recurrence following radical prostatectomy segregated by body mass index. PSA, prostate-specific antigen. Reproduced, with permission, from Freedland SJ et al.* J Clin Oncol. *2004;22:446-453.*[36]

Increased BMI and Risk of Dying of Prostate Cancer

The majority of the epidemiologic literature suggests that, although obesity *may* be related to the risk of prostate cancer, it is clearly associated with an increased risk of dying from prostate cancer. Although results from small studies have been conflicting,[39-41] data from larger studies have consistently demonstrated an association between increased BMI and risk of dying from prostate cancer.[7,15,42,43] Two large prospective studies deserve particular attention. In 1959 and again in 1982, the American Cancer Society enrolled a cohort of patients 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.[43] Together, these studies followed 816,268 men, among whom there were 5212 prostate cancer deaths. Both CPS-I and CPS-II reported that obese men (BMI >30 kg/m^2) were significantly more likely to die of prostate cancer: 27% increased risk of prostate cancer death in CPS-I and 21% increased risk in CPS-II.[43] More data from CPS-II were recently published showing that severely obese men (BMI >35 kg/m^2) were at even greater risk for prostate cancer death, having a 34% higher risk relative to normal-weight men.[7] Moreover, a recent study found that obesity in adolescence also increases the risk of dying of prostate cancer, suggesting that events involved in prostate carcinogenesis and progression may occur early in life.[44]

WHR and Prostate Cancer

WHR, the ratio of waist-to-hip circumference, provides an estimate of abdominal obesity. In general, a WHR value greater than 0.9 is considered obese.[13] The significance of abdominal obesity is that it more closely correlates with various hormonal and metabolic sequelae of obesity, as well as the risk of other comorbid diseases, such as heart disease and diabetes.[45-47] Few studies have examined WHR in terms of its relationship to prostate cancer. One study among men in China found that those in the highest quartile of WHR had an almost 3-fold increased risk of prostate cancer.[24] Interestingly, despite a significant relationship between WHR and prostate cancer risk, the authors found no association between BMI and prostate cancer risk, suggesting that abdominal obesity as measured by WHR may be more closely related to the development of prostate cancer than other more general measurements of obesity.

Insulin

Obesity is associated with insulin resistance and non–insulin-dependent diabetes mellitus.[5,48] It has been hypothesized that insulin resistance may be related to prostate cancer.[49] Studies examining the relationship between insulin resistance and/or diabetes and prostate cancer risk have shown mixed results. For example, using data from CPS-I, Will and colleagues[50] found no relationship between diabetes and the risk of prostate cancer development, except among men who had diabetes for 5 years or longer.

On the other hand, Giovannucci and colleagues,[51] using data from the Health Professionals Follow-up Study, found that diabetes was associated with a decreased risk of prostate cancer and that the longer one had diabetes, the greater the risk reduction. Other studies found that insulin resistance, diabetes, and/or higher insulin/glucose levels either increase,[52-55] decrease,[56-58] or have no effect[59,60] on the risk of prostate can-

cer. Interestingly, certain polymorphisms in the insulin gene have been associated with an increased risk of prostate cancer.[61] Given the amount of conflicting data in the literature, it is difficult to determine the true impact of insulin resistance and/or diabetes on prostate cancer.

IGF Axis

IGF-I is a peptide growth factor and a potent mitogen for the growth of androgen-responsive and androgen-independent human prostate cancer cell lines.[62] IGF-1 activity is modulated by high-affinity IGF-binding proteins (IGFBPs 1-6).[63] The IGFBPs collectively bind and inactivate IGF-1, resulting in lower levels of free (bioavailable) IGF-1. Circulating levels of IGFBP-1 and -2 are nutritionally regulated.[64] Obesity is associated with increased free or bioactive IGF-1.[11,65] IGF-1 plays a pivotal role in stimulating cell proliferation, regulating differentiation, and reducing apoptosis.[64,66] Tissue levels of IGF-1 appear to be a critically important factor during initiation and progression of prostate cancer.[64,67]

Multiple epidemiologic studies have found a direct correlation between serum IGF-1 levels and the risk of prostate cancer.[68-71] A recent meta-analysis of studies examining hormonal influences on the risk of prostate cancer concluded that higher serum IGF-1 levels were significantly associated with an increased prostate cancer risk.[72] However, it should be noted that the majority of studies that found this association were performed either before widespread PSA screening,[68] during periods of widespread PSA screening but with a high PSA cutoff point for biopsy (>10 ng/mL),[71] or in countries in which PSA screening is not particularly common.[69,70] Thus, men in these studies had tumors detected at more advanced stages than is commonly seen in the United States today. Indeed, a follow-up investigation of participants from the Physicians' Health Study, a prospective study of nearly 15,000 male physicians in the United States, found that IGF-1 and IGFBP-3 levels correlated with advanced-stage prostate cancer but not with early, clinically localized prostate cancer.[73]

Multiple epidemiologic studies have found a direct correlation between serum IGF-1 levels and the risk of prostate cancer.

These findings raise the possibility that the majority of men in these studies who later received a diagnosis of prostate cancer already had prostate cancer at the time of serum collection and, thus, higher IGF-1 levels may not be etiologic in prostate cancer but rather may function as a tumor marker. This hypothesis was supported by a recent investigation within a case-control study of men in the United States. The authors found no relationship between IGF-1 or IGFBP-3 levels and prostate cancer risk but did find that, among cases, but not controls, serum IGF-1 levels steadily increased over time.[74] Some authors have even examined whether IGF-1 levels can be used, along with PSA measurement, to help diagnose prostate cancer; results have been mixed.[75,76] However, the fact that IGF-1 levels increase after radical prostatectomy[77] argues against IGF-1 as a useful tumor marker. Further studies are needed to determine whether elevated IGF-1 levels are etiologic in prostate cancer development or merely function as a tumor marker.

Free IGF-1 levels are regulated by serum levels of the IGFBPs, of which IGFBP-3 predominates. Whereas most studies that examined the IGF axis and prostate cancer risk found an increased IGF-1 level to be associated with prostate cancer, the results when examining serum IGFBP-3 levels are less clear. Using data from the Physicians' Health Study, Chan and colleagues[68] found that IGFBP-3 level was not associated with prostate cancer risk. However, after adjustment for IGF-1 levels, higher IGFBP-3 levels, and thus lower free IGF-1 levels, were associated with a decreased risk of prostate cancer. This is in contrast to a nested case-control study within the Northern Sweden Health and Disease Cohort Study, which found that higher IGFBP-3 levels were associated with an increased risk of prostate cancer. After controlling for IGF-1 levels, however, no significant relationship was seen.[69]

Further studies are needed to determine whether elevated IGF-1 levels are etiologic in prostate cancer development or merely function as a tumor marker.

Leptin

Leptin is a polypeptide hormone produced by adipocytes. In general, increased numbers of adipocytes are associated with higher serum leptin levels. The normal physiologic role of leptin is in appetite control.[78] A direct link between leptin and obesity exists in that mice lacking or with mutations in either the leptin or lep-

tin receptor genes are phenotypically obese.[78] In humans, mutations in the leptin receptor and leptin genes have been described in some obese patients, although most obese persons have elevated leptin levels in line with their degree of adiposity.[79]

The link between leptin and body weight was further demonstrated when a double-blind, randomized, controlled trial found that administration of recombinant leptin resulted in greater weight loss than did placebo among obese patients.[80] In vitro, leptin stimulates growth of the androgen-independent cell lines DU145 and PC-3, but not the androgen-sensitive cell line LNCaP.[81,82] In addition, human prostate cancers express the leptin receptor.[83] Studies examining the relationship between serum leptin levels and risk of prostate cancer have produced mixed results. Some have found a positive correlation between serum leptin levels and prostate cancer risk,[83,84] whereas others have found no association.[54,85,86] Interestingly, the few studies that examined leptin levels among men with prostate cancer found that higher leptin levels were associated with larger tumors, higher-grade tumors, and more advanced tumors.[84,87] Thus, leptin may be more useful as a prognostic marker among men with prostate cancer than as a predictor of who will develop prostate cancer; however, more studies are needed to confirm these findings.

Dietary Fat

Significant preclinical data have linked dietary fat to prostate cancer. The fatty acid consumed in the greatest quantity in the Western diet is linoleic acid (omega-6 polyunsaturated fatty acid), which is a known growth factor for androgen-dependent and androgen-independent prostate cancer cell lines.[88,89] In human xenograft models, a low-fat diet results in slower androgen-sensitive prostate cancer growth and can delay progression from androgen-sensitive to androgen-insensitive growth.[89-91] Changes in dietary fat intake have been linked to changes in IGF-1 levels, suggesting one possible mechanism for the relationship between dietary fat and prostate cancer.[92] Two genes consistently found to be upregulated in human prostate cancer relative to normal states, fatty acid synthase and alpha-methylacyl-CoA racemase, are involved in fatty acid production and beta-oxidation, respectively.[93-96]

As men in underdeveloped nations have adopted a more Western lifestyle and diet, the incidence and mortality of prostate cancer in those areas has increased.

Globally, prostate cancer incidence and mortality rates are associated with a Western lifestyle and diet; however, whether this reflects increased fat intake or decreased intake of various protective products, such as soy and lycopene, is unclear.[97] Comparison of diets between countries with low and high incidences of prostate cancer suggests that one of the strongest dietary risk factors for the development of prostate cancer is intake of animal products.[98-100] Moreover, as men in underdeveloped nations have adopted a more Western lifestyle and diet, the incidence and mortality of prostate cancer in those areas has increased.[97]

Many epidemiologic studies have investigated the relationship between dietary fat intake and human prostate cancer. A complete review of the epidemiologic literature regarding the relationship between prostate cancer and all the various components of dietary fat—animal versus vegetable, unsaturated versus saturated, omega-3 versus omega-6, monounsaturated versus polyunsaturated—is beyond the scope of this review. More details regarding dietary fat and prostate cancer can be found in 2 excellent reviews by Kolonel and colleagues[101] and Moyad.[102] Here, we focus on total and animal fat intake.

Most case-control studies have demonstrated a positive relationship between dietary fat intake and prostate cancer risk.[102] However, case-control studies have the limitation of recall bias: dietary recall can result in inaccurate information regarding true exposure history.[103,104] Therefore, more accurate information regarding the role of dietary fat in prostate cancer risk can be obtained from prospective cohort studies in which dietary information is assessed at study entry and/or longitudinally. The majority of large prospective cohort studies have shown no association between dietary total fat intake and prostate cancer risk.[18,105-109] However, some studies have found a positive but not statistically significant association between animal fat intake and prostate cancer risk.[110] Others have found a statistically significant relationship between the two.[111] Interestingly, one study found that animal fat intake, but not total fat intake, was correlated with prostate cancer risk.[112] This suggests that it may not be the fat itself but rather the preparation of the food and the toxins formed during the cooking process that are involved in carcinogenesis.[113,114] Several studies found that animal and/or total fat intake was related to the risk of prostate cancer death.[42,115] Taken together, these data relating dietary

fat and prostate cancer suggest a possible relationship with prostate cancer development but a stronger relationship with advanced disease and risk of prostate cancer death.

Conclusion

Obesity is clearly an epidemic in American society and is linked to numerous chronic medical conditions. The relationship among obesity, its physiologic sequelae, and the risk of prostate cancer is unclear. What is clear is that obese men are at significantly greater risk for dying of prostate cancer. Attempts to reduce obesity in the general population are necessary. Whether lifestyle alterations after the diagnosis of prostate cancer can alter the natural history of the disease remains to be determined.[116] Further studies are needed to determine the molecular basis for increased prostate cancer mortality among obese men. ■

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Main Points

- Results of studies examining body mass index (BMI) and prostate cancer risk are conflicting.
- Larger studies, notably the Cancer Prevention Studies of the American Cancer Society, have consistently demonstrated that obese men have a significantly greater chance of dying of prostate cancer than non-obese men.
- The data on the impact of insulin resistance and diabetes on prostate cancer are conflicting: some studies have found that insulin resistance, diabetes, and/or higher insulin/glucose levels increase the risk of prostate cancer, whereas others have reported a decreased risk or no effect on risk at all.
- Although many epidemiologic studies have found a direct correlation between higher serum insulin-like growth factor (IGF)-1 levels and increased prostate cancer risk, most such studies were performed before prostate-specific antigen screening was widespread or in places in which it is not common; thus, the participants may have already had cancer during sampling. The resulting hypothesis that high IGF-1 level may be a tumor marker rather than an etiologic factor has been supported by some authors, but more research is necessary.
- A direct link exists between leptin level and obesity, but the results are mixed as to leptin's link to prostate cancer risk and its usefulness as a predictor. However, a few studies have shown higher leptin levels to be associated with larger tumors, higher-grade tumors, and more advanced tumors, making leptin a potential prognostic marker in patients with prostate cancer.
- Although the Western diet appears to have a role in prostate cancer globally, the mechanism behind the relationship is unclear; the evidence suggests that dietary fat has a possible link to prostate cancer development but a stronger link with advanced disease and risk of prostate cancer death.

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