Perspective

Obesity, Endogenous Hormone Metabolism, and Prostate Cancer Risk: A Conundrum of "Highs" and "Lows"

Perspective on Neuhouser et al., p. 279

Rudolf Kaaks[1] and Pär Stattin[2]

Abstract

This perspective on the report by Neuhouser et al. (beginning on page 279 in this issue of the journal) examines the associations that have been observed between body mass index, serum insulin, preexisting diabetes, androgen metabolism, and prostate cancer risk. Based on data of the Prostate Cancer Prevention Trial, the observations by Neuhouser et al. plus findings from other studies suggest a complex mix of higher and lower risks for high- and low-grade cancer in association with obesity and endogenous hormone metabolism. *Cancer Prev Res; 3(3); 259–62. ©2010 AACR.*

Age-standardized incidences of prostate and many other cancers are more than 20-fold higher in affluent, industrialized countries than in developing countries. These increased cancer incidences are likely a consequence of differences in life-style, including diet and physical activity. Adverse nutritional energy balance, as reflected by excess body weight and associated alterations in metabolism, is becoming increasingly implicated in cancer development (1). For prostate cancer, however, epidemiologic studies initially did not identify excess weight as a major risk factor and generally have identified thus far only a few specific life-style–related or metabolic risk factors for this cancer. The paucity of identified risk factors may be due to the introduction of prostate-specific antigen (PSA) testing in "Westernized" societies during the 1990s. PSA testing has caused a dramatic increase in the incidence of small and relatively innocuous, low–Gleason grade prostate tumors and thus changes in the mix of high and low Gleason grade among diagnosed cases. More recent epidemiologic studies with more detailed accounting of these complexities increasingly have found that excess weight, often expressed as elevated body mass index (BMI, or weight divided by the square of height), is related to an increased risk of high-grade prostate cancer and prostate cancer mortality but also possibly to a reduced risk of low-grade prostate cancer (2).

Most biological mechanisms hypothesized to underlie the relationship between adiposity and tumor development involve adiposity-related changes in metabolism

Authors' Affiliations: [1]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany and [2]Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå, Sweden

Corresponding Author: Rudolf Kaaks, Division of Cancer Epidemiology, Im Neuenheimer Feld 280, German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany. Phone: 49-0-6221-422200; Fax: 49-0-6221-422203; E-mail: r.kaaks@dkfz.de.

and endogenous hormone levels (1). An important specific metabolic consequence of obesity, particularly when combined with physical inactivity, is a reduced tissue response to insulin, especially in terms of reduced uptake of glucose. This insulin resistance leads to chronically elevated blood levels of insulin, which is a growth-enhancing hormone and thus is a biologically plausible risk factor for cancer development and progression (3, 4).

The relationship between hyperinsulinemia and prostate cancer risk has been directly examined thus far in only a few prospective studies. A study in Northern Sweden (5) found that C-peptide, a marker for pancreatic insulin secretion, had a statistically significant inverse relationship with the risk of nonaggressive prostate cancer but also a statistically nonsignificant direct association with the risk of aggressive disease. Furthermore, higher blood levels of leptin, glycated hemoglobin (HbA1c), and glucose (both fasting levels and levels 2 hours after an oral glucose load) all showed statistically nonsignificant inverse associations with the risk of nonaggressive tumors and no association with the risk of advanced tumors (5).

Another of these few prospective studies is reported in the present issue of the journal by Neuhouser et al. (6). They report results of new analyses of prostate cancer risk in the Prostate Cancer Prevention Trial (PCPT), a large-scale randomized trial of finasteride, an inhibitor of prostatic 5-α reductase, in over 18,000 men (7). Frequent examinations of all trial participants including digital rectal examinations, PSA measurements, prostate biopsies, and centralized histologic characterization of all prostate cancers make the PCPT an exceptional setting for prospective studies of the causes of prostate cancer. High insulin levels, as reflected by increased serum levels of C-peptide, were associated with a significantly increased risk of high-grade but not low-grade prostate cancer in the PCPT placebo arm. Together with results from two other recent prospective studies, in which C-peptide levels also were directly associated with prostate cancer mortality (8) and incidence of high-grade

prostate cancer (9), these results suggest a role of hyperinsulinemia in the development and progression of high-grade prostate cancer. It is intriguing that C-peptide was not associated with the risk of high-grade prostate cancer but was inversely associated (although not significantly) with the risk of low-grade cancer in the finasteride arm. Leptin, which did not interact with finasteride, was not associated with high-grade prostate cancer but was inversely associated with low-grade prostate cancer in the combined arms.

These recent observations raise two key questions. First, what mechanism explains the heterogeneity of associations of BMI and hyperinsulinemia with high- and low-grade prostate cancers? Second, what explains the null relationship between hyperinsulinemia and high-grade prostate cancer in men treated with finasteride?

One tentative explanation for the first level of heterogeneity, i.e., different risk associations between low- and high-grade cancers, could be diagnostic bias. This aspect has received increasing attention after the primary publication of PCPT findings in 2003, which reported an overall decreased prostate cancer risk of 25% but also a surprising increased risk of high-grade prostate cancer in the finasteride arm (7). Finasteride also produced a 25% decrease in average prostate volume and a 50% decrease in serum PSA values. Subsequent analyses indicated that the increase in high-grade prostate cancer could have been entirely due to improved diagnosis, especially of high-grade tumors, following reductions in prostate volume in the finasteride arm (10). This improvement in diagnosis could be due to increased PSA specificity for prostate cancer because of reduced contributions to circulating PSA from benign prostatic hyperplasia (11) and due to increased biopsy sensitivity for prostate cancer because biopsy sampling density is increased in smaller prostates (10). Independently of the PCPT, some studies have shown that these finasteride-related improvements in test validity might lead to preferential detection especially of larger, high-grade tumors, over small and low-grade tumors (12, 13). Contrary to merely a preferential *detection* of high-grade tumors in smaller prostates, however, there is evidence from radical prostatectomy specimens that the occurrence of high-grade tumors might be *actually* higher in smaller prostates (14).

An increasing number of studies have shown that obesity, high insulin, and type II diabetes mellitus are associated with increased prostate volume but, paradoxically, with lower PSA levels (15–17). The inverse relationship between obesity and PSA, in spite of a larger prostate volume, could be caused by hemodilution resulting from larger plasma volumes among obese men (18). Reduced PSA values likely decrease the probability of men undergoing prostate biopsies and thus cancer detection, and increased prostate volume may especially diminish the probability of detecting small, low-grade tumors in prostate biopsies. These combined effects could lead to a negative bias in relative risk estimates, especially for low-grade prostate tumors, in relation to BMI or adiposity-related metabolic risk factors. It is conceivable that

these effects also could explain the heterogeneous associations of BMI or adiposity-related metabolic factors with risks of high- and low-grade prostate cancer. Although extensive data on prostate volume and blood PSA levels are available for PCPT participants, Neuhouser et al. (6) did not report the correlations of these variables with BMI, C-peptide, or leptin in the two PCPT arms, nor did they address the question of whether these variables could explain the heterogeneity of the relationship of C-peptide with low- and high-grade tumors. Neuhouser et al. (6) did report, however, that accounting for prostate volume did not resolve the difference between the finasteride and placebo arms in terms of the C-peptide–prostate cancer relationship.

Preexisting diabetes was associated with reduced risks of both low-grade tumors (reduced, 46%) and high-grade tumors (28%) in the PCPT (19). In contrast, obesity (BMI, ≥30) was associated with a modest (18%) reduction in the risk of low-grade prostate cancer (Gleason, <7) but with increased risks of high-grade cancer (29% for the Gleason sum of ≥7; 78% for the Gleason sum of 8-10), compared with normal weight (BMI <25). Mutual adjustments between obesity and diabetes did not alter these relative risk estimates, which is counterintuitive given the generally strong relationship between type 2 diabetes and obesity. Results of other epidemiologic studies also show that, in contrast to excess body weight (which is associated with an increased risk of high-grade but a possible reduced risk of low-grade prostate cancer), diabetes was associated with reductions in the risks of both nonadvanced (low-grade/early clinical stage) or advanced (high-grade/advanced clinical stage) prostate cancer (20–23).

Contrary to the present findings on C-peptide in the PCPT (6), the associations of risks for low- and high-grade prostate cancer with diabetes, BMI, and waist circumference did not differ significantly between the finasteride and placebo arms of the PCPT (19). There was a relatively low correlation between C-peptide and BMI in the PCPT [correlation coefficient (r) = 0.25], possibly because of the use in the PCPT of serum from nonfasting men. In studies involving fasting blood, correlations of insulin or C-peptide with BMI generally were higher (e.g., r = 0.49 in the study by Stocks et al.; ref. 5). The lower correlation between C-peptide and BMI in the PCPT may have increased the probability that a comparison of the prostate cancer risks associated with these two factors seemed to be "incoherent," as a result of chance fluctuations; on the other hand, strongly correlated factors would be expected *a priori* to have similar associations with disease outcomes. Studies within other randomized trials may provide further information on the possible effect of the interaction between 5-α-reductase inhibition and obesity, hyperinsulinemia, or other obesity-related metabolic factors on prostate cancer risk.

Like insulin, the androgens testosterone and dihydrotestosterone (DHT) have long been known to play an important role in prostate gland development and prostate cancer progression and so are suspected of involvement

in earlier stages of prostate cancer development. Sex hormone–binding globulin (SHBG), a carrier protein that specifically binds circulating testosterone and DHT and reduces their availability to tissues, correlates inversely with BMI. This inverse correlation is due mostly to increases in serum insulin, which inhibits hepatic SHBG synthesis. Total (bioavailable plus chemically bound/unavailable) testosterone also correlates inversely with both BMI and insulin. The latter inverse relationship can be explained by long-loop feedback inhibition of pituitary luteinizing hormone secretion by bioavailable (non-SHBG bound) testosterone, which leads to reduced testicular androgen synthesis. Through this mechanism, bioavailable testosterone is kept relatively constant over a wide range of BMI (reviewed in ref. 24). In obese men (BMI, >30), however, not only are total testosterone and SHBG, luteinizing hormone pulse amplitude, and diurnal luteinizing hormone levels reduced, but bioavailable testosterone levels also are reduced.

A recent pooled reanalysis of prospective studies indicated no relationship between serum total testosterone and the risk of prostate cancer overall or by tumor stage or grade (25). Nevertheless, this analysis showed a weak inverse relationship between SHBG and prostate cancer risk. The interpretation of the latter association remains unclear. As discussed above, reductions in SHBG associated with excess weight do not generally correlate with higher levels of bioavailable testosterone, and this analysis showed no relationship of prostate cancer risk with serum levels of non-SHBG–bound testosterone.

These various observations collectively argue against a role for total or bioavailable serum androgen levels in mediating the contribution of excess weight to prostate cancer risk. These data, however, do not altogether rule out a role for androgens in prostate cancer development (26). Current evidence suggests (*a*) that conversion of testosterone into DHT by 5-α reductase may be the key determinant of androgenic action within the prostate and (*b*) that most intraprostatic DHT is formed locally within the prostate. It is conceivable that variations in intraprostatic DHT synthesis do influence prostate cancer development, although they have little correlation with circulating androgen levels. Some analyses of PCPT data support this hypothesis. Indeed, after accounting for finasteride effects on prostate volume, finasteride in the PCPT was associated with a 22% reduction in the risk of the most frequently detected high-grade cancer, i.e., Gleason score 7, and with an even greater reduction in the risk of Gleason score 5 or 6 cancers (27). Furthermore, an in-depth histopathologic analysis of subsets of PCPT prostate tumors (28) indicated that finasteride led to earlier detection of high-grade tumors, which, however, seemed to be reduced in the finasteride (versus placebo) group. These latter observations could be an indication that analyses that properly account for possible diagnostic biases may find that 5 α-reductase inhibition has a genuine chemopreventive effect against high-grade prostate cancer development, possibly through its chemosuppressive effect on small, low-grade tumors.

About the second level of heterogeneity, i.e., insulin-related risks in the finasteride versus the control arm of the PCPT, the absence of an association between C-peptide levels and prostate cancer risk in the finasteride arm may be related to the overall endocrine effect of 5-α reductase inhibition. In other studies (29), finasteride has both increased serum testosterone levels and decreased BMI, but Neuhouser et al. (6) did not observe such overall effects in the first 2 years of observation in the PCPT. Nevertheless, because testosterone decreases with age whereas BMI and insulin generally tend to increase, one could speculate that PCPT men, especially older ones, who were more likely to harbor cancer in their prostates, could have benefitted from a finasteride-induced decrease in insulin levels, as suggested in earlier studies (29).

In summary, epidemiologic observations depict a complex pattern of associations involving adiposity, serum insulin levels, and preexisting diabetes and increased and decreased risks of high- and low-grade prostate cancer. Overall, current evidence points strongly to a relationship between excess body weight and a greater risk of high-grade prostate cancer and, possibly, a reduced risk of low-grade cancer. These relationships, particularly that involving low-grade cancer, however, carry some suspicion of distortion due to diagnostic biases. The few prospective studies that directly addressed insulin and prostate cancer risk suggest that their relationship may differ for low- and high-grade tumors, as it does for BMI. Paradoxically, however, preexisting diabetes, which is strongly related to excess weight and increased insulin levels for long periods before and after diagnosis, has been found most often to be associated with a reduced risk of both low- and high-grade prostate cancer. This paradox might be due to the fact that the vast majority of diabetes patients are type II diabetics, in whom metabolic status may move gradually from hyperinsulinemia to endogenous insulin deficiency, thus blunting insulin effects in increasing prostate cancer risk. Consistent with this idea, one large prospective study showed a slightly increased prostate cancer risk during the first 3 years but a reduced risk >4 years after diagnosis of diabetes (21). It is also possible that certain diabetes medications reduce prostate cancer risk (30). A further possibility is that the relationships of prostate cancer risk with diabetes and with adiposity involve different predominant mechanisms.

Although circulating androgen levels do not seem to affect prostate cancer risk, intraprostatic DHT levels may be a key factor in prostate tumor development and prognosis. Very little is known, however, about how life-style factors and excess body weight can influence intraprostatic androgen levels and actions. The suggestion that finasteride treatment may influence the association of circulating insulin with the risk of low- or high-grade prostate cancer (decreasing the insulin-associated risk of either) is an important hint that insulin, or a closely correlated metabolic factor, could be involved in mediating effects of nutritional energy balance on intraprostatic androgen metabolism or action effects that would be

blunted by a 5-α reductase inhibitor. Further studies of the effects of energy balance on intraprostatic androgen metabolism and relationships of these factors with risks of low- and high-grade prostate cancer should be high on the agenda of future research. It is time to solve the conundrum of "highs" and "lows," the virtually inscrutable mix of higher and lower risks of high- and low-grade disease, surrounding the relationship of obesity and endogenous hormone metabolism with prostate cancer development.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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