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Metabolic Risk Factors in Prostate Cancer

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Abstract

The biology of prostate cancer is influenced by the metabolic profile of each individual. We examine the evidence available interlinking prostate cancer with obesity, diabetes, and other metabolic syndrome components.

Keywords

prostate cancer; glucose; insulin; IGF-1; testosterone; triglycerides; cholesterol

Metabolic syndrome (metS) and prostate cancer (CaP) remain two growing health problems affecting millions of men. While various metS definitions exist,1 according to the National Cholesterol Education Program's Adult Treatment Panel III,2 it is diagnosed by ≥3 of the following components: central obesity, raised triglycerides/treatment thereof, reduced high-density lipoprotein (HDL) cholesterol/treatment thereof, hypertension/treatment thereof, and hyperglycemia/treatment thereof. With mounting evidence linking CaP with various metS components, future research must be directed towards combating both diseases and understanding their interplay.

Towards this end, Van Hemelrijck et al. examined the relationship between CaP risk and various metS components in the large prospective AMORIS cohort from Sweden: >200,000 CaP-free men of varying ages were followed for ≥7 years until death, the study closing date, or CaP diagnosis, which occurred in 5,112 men. The primary outcome was CaP risk as a function of baseline triglycerides, total cholesterol, and glucose levels drawn within ten years prior to cohort entry, with >60% of measurements being fasting. The authors found men with higher glucose had lower CaP risk. Moreover, elevated triglycerides were associated with greater CaP risk, but only in men with high glucose. Lastly, the authors graphically showed non-CaP-related mortality may alter the observed associations between metabolic factors and CaP. Given that men who die of other causes are no longer at risk for CaP, one must account for this competing risk. The authors suggest that because of this competing risk, the association between high glucose and reduced CaP risk may be overestimated, while the association between high triglycerides and elevated CaP risk in hyperglycemic men may be underestimated.

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Van Hemelrijck et al.'s results provide a reminder not to ignore the competing effects of non-CaP-related mortality on CaP risk. Diabetics in particular, with their concomitant higher risk of cardiac disease and mortality, may be at lower CaP risk because they do not live long enough to develop CaP. Though this association between high glucose and lower CaP risk may be overestimated, it did not disappear entirely after adjustment for non-CaP-related mortality, suggesting the associations have a biological explanation.

Importantly, Van Hemelrijck et al.'s findings reinforce the hypothesis that CaP development and growth relies on various metabolic factors. These include but are not limited to glucose, insulin, insulin-like growth factor-1 (IGF-1), testosterone, triglycerides, and cholesterol. Marked alterations in these factors are common in men with obesity, diabetes, and metS. Although the exact interplay among these factors and CaP remains unclear, they all have important clinical implications for future directions in CaP research and ultimately CaP prevention and treatment. Though Van Hemelrijck et al. did briefly mention these factors, they all are worthy of further discussion in the context of CaP risk.

Glucose, Insulin, and IGF-1

The association between high glucose and reduced CaP risk found by Van Hemelrijck et al. underscores the fact that diabetes (characterized by high fasting glucose) is consistently linked to lower CaP risk.1 In one multiethnic cohort of >86,000 men, diabetics had significantly lower CaP risk and significantly lower PSA levels versus non-diabetics.3 Another study noted time since diabetes diagnosis significantly affected CaP risk in a cohort of >72,000 men, with a positive association between CaP risk and being diagnosed with diabetes <4 years prior to CaP and an inverse association for men with diabetes >4 years.4 This fits with the natural history of type 2 diabetes: persistently elevated glucose leads to an initial insulin rise, then eventually to insulin resistance, diabetes, and ultimately low insulin due to damaged pancreatic beta-cells. Since elevated insulin is strongly implicated in CaP growth and mortality,5 long-standing diabetics, with their lower insulin, may be protected from CaP.

The clinical implications of this protective effect of diabetes on CaP are controversial. As diabetic men have lower PSA levels than non-diabetic men,3 a detection bias may exist in CaP screening that may explain the decreased risk. Diabetic men may not reach the PSA threshold for biopsy and thus have delayed diagnosis. A nested case-control study from the Prostate Cancer Prevention Trial (PCPT),6 however, examined men who underwent biopsy-determined CaP presence or absence regardless of PSA and found decreased CaP risk in diabetics. Additionally, the same study showed a 28% reduced high-grade CaP risk in diabetics versus non-diabetics,6 which is unexpected if diabetic men truly suffered from delayed diagnosis. Thus, the meaningfulness of lower PSA in diabetic men remains unclear.

Closely related to insulin, IGF-1 is a CaP mitogen. Clinical data strongly implicate IGF-1 in increased CaP risk.7 A recent meta-analysis encompassing 42 studies and >7,400 CaP cases confirmed a significant positive association between elevated IGF-1 levels and CaP risk, with weak evidence of an association with advanced-stage disease.7 Additional evidence comes from translational research in mouse models highlighting its effect on cellular proliferation and inhibition of apoptosis. Transgenic mice with genetically high IGF-1 concentrations developed spontaneous prostate tumors.8 Moreover, IGF-1 knockout mice demonstrated decreased prostate size and decreased prostatic androgen-receptor expression, and thereby attenuated prostatic androgenic response.9 IGF-1 may therefore affect CaP growth by serving as a link between the insulin and androgen axes.

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Testosterone

The dependence of CaP on androgens is well-established. Not surprisingly, therefore, conventional wisdom has thought testosterone should be associated with CaP risk. Although initial studies suggested CaP risk increased with increasing circulating testosterone,10 the Health Professionals Follow-up Study11 showed divergent effects of testosterone on tumor grade. Low total and free testosterone were inversely associated with low-grade tumors but positively associated with high-grade tumors.11 A possible explanation for this relationship is that high-grade tumors are more aggressive and may be more androgen-independent than low-grade tumors, thereby continuing to progress despite the relative lack of testosterone. However, a recent meta-analysis of 18 prospective studies found no association between CaP risk and serum endogenous sex hormones levels, nor any differentiation of effect by tumor grade.12

Notably, testosterone has also been linked to diabetes,13 triglyceride levels,14 and metS,14 which has key implications in determining CaP risk. A meta-analysis of studies linking diabetes and sex-steroid hormones found men with higher testosterone had 42% decreased diabetes risk versus men with lower levels.13 Additionally, a recent meta-analysis of 21 studies found testosterone replacement therapy in hypogonadal men drastically improved many metS components, including reduced triglycerides, glucose, insulin resistance, and waist circumference, and increased HDL levels.14 These effects are also seen in men undergoing hormonal therapy for CaP (i.e. the opposite of testosterone replacement) who are at greater risk for insulin resistance, obesity, and altered lipids.15 Collectively, this evidence suggests that testosterone, due to crucial interplay with other CaP metabolic risk factors, may be a critical mediator in the regulation and treatment of not only metS and its components, but also CaP.

Triglycerides

High triglycerides may be a CaP risk factor, though results are mixed. While Van Hemelrijck et al. found a positive association between high triglycerides and CaP risk in men with high glucose levels, other investigators have found no relationship between high triglycerides and CaP risk.16 To explain these discrepancies, the frequent co-occurrence of hypertriglyceridemia with insulin resistance and diabetes has been hypothesized as a confounding factor.1, 16 One study showed that while diabetic men with ≥2 other metS components had a 23% reduced CaP risk, non-diabetic men with two metS components had a 37% significantly *increased* risk versus men without any metS components.16 The protective effect of insulin resistance and diabetes may therefore obscure the effects of hypertriglyceridemia and, in general, the overall effects of metS, on CaP risk. Moreover, to help explain why Van Hemelrijck et al. found a positive association between high triglycerides and CaP risk only in hyperglycemic patients, other confounding factors not included in their study such as obesity may be involved. Many patients with high triglycerides and diabetes also have obesity, which, while inconsistently associated with CaP risk,17 has been clearly linked with aggressive CaP18 and worse cancer-specific survival.19

Cholesterol

As the molecular skeleton of all steroids, including androgens, cholesterol has been studied extensively in CaP. Basic science experiments found high cholesterol levels are linked to increased tumor proliferation and angiogenesis and decreased cell apoptosis.20 Clinical studies, however, suggest elevated cholesterol is associated only with high-grade CaP.21 One large study from the PCPT placebo arm found a strong correlation between lower cholesterol and lower risk of high-grade CaP.21 Moreover, the strongest evidence to support the benefit of statins come from four large prospective studies showing similar reductions in

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advanced CaP risk in statin users, but not overall CaP risk.22 Thus, while Van Hemelrijck et al. did not find an association for high cholesterol with overall CaP risk, their study did not distinguish high-grade from low-grade tumors.

Conclusion

CaP risk has been significantly linked to numerous metabolic factors, which in and of themselves have varying degrees of interplay. While one future research goal is to better understand the molecular underpinnings of such interplay, an eye must always be turned to the epidemics of metS, obesity, and diabetes in addition to CaP. Statins, diet, and exercise certainly provide non-toxic preventive strategies against these public health concerns, but will they be enough? Certainly the data from Van Hemelrijck et al. remind us CaP exists within a person and factors influencing CaP risk may also influence non-CaP-related morbidity and mortality. Thus, we are reminded that all patients whether at risk or who have actual CaP can benefit from advice about healthy eating, weight loss, and exercise. Whether such approaches alter the course of established CaP or prevent CaP is unclear, though they are unlikely to be harmful.23 With metS, obesity, and diabetes becoming increasingly rampant, concern for CaP, not to mention significant non-CaP-related morbidity and mortality in the next generation demands a sense of urgency today.

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